CVS

Pathology

PSYCHOPATHS

18-2-08

References were Basic Pathology 7th Edition + Online references

Histology of the Heart , 3 layers

1. **Endocardium:** lines ***the inner surface of the heart***, consists of a ***single, thin layer of endothelium*** overlying a continuous basement membrane covering the inner chambers, cardiac valves, chordae tendonae and the papillary muscle. .

2. Myocardium: ***the intermediate layer***, consists of ***a unique form of striated muscle termed cardiac muscle***, which is embedded in a connective tissue framework with numerous capillaries.

3. Epicardium: (also called the pericardium) is the ***outermost cardiac layer***, it is ***lined by a thin layer of mesothelium*** that rests on a layer of connective tissue, which merges with the connective tissue of the myocardium.

Ischemic Heart Disease

Caused by:

an imbalance between the myocardial oxygen demand and the blood supply.

Most Common Cause of the imbalance:

Narrowing of Coronary artery by atherosclerosis , that's why its often termed *coronary heart disease* or *coronary artery disease*.

Nature of resulting disease is determined by:

a) The degree of coronary insufficiency

b) the rapidity of onset

c) the degree of collateral circulation

It may lead to one of the following 4 syndromes:

(1) various forms of angina pectoris (chest pain) → Acute

(2) acute myocardial infarction (MI) → Acute

(3) sudden cardiac death → Acute

(4) chronic ischemic heart disease with congestive heart failure → Chronic

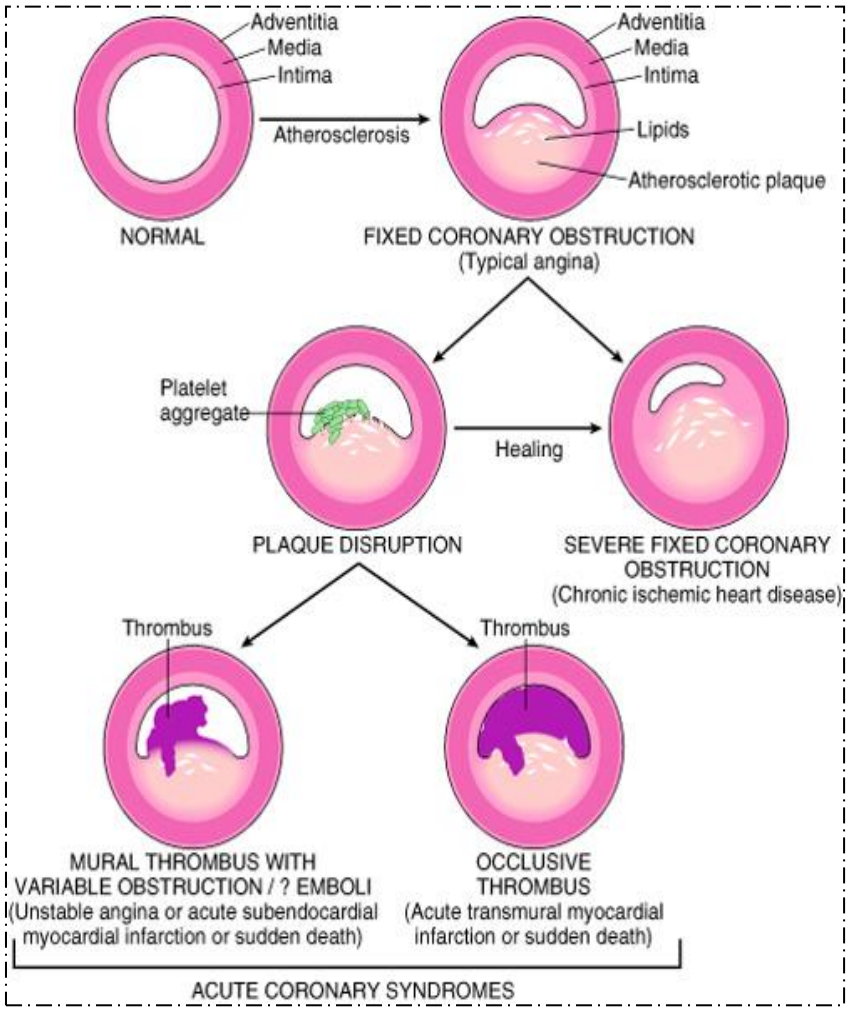
Ischemic heart disease is the single most common cause of death in economically developed countries of the world, including the United States and western Europe, where it is responsible for about **one third of all deaths.**

Epidemiology:

coronary atherosclerosis may occur at any age but are most common in older adults, *Peak incidence: 60y for males and 70y for females.* ***Men are more commonly affected than women until the ninth decade, by which time the frequency of coronary artery disease is similar in both sexes*.** Factors that contribute to the development of coronary atherosclerosis include

hypertension, diabetes mellitus, smoking, and high levels of low-density lipoprotein cholesterol

Genetic factors **undoubtedly play an important role in the development of coronary atherosclerosis.**



Atherosclerosis of Coronary artery is the leading cause of Ischemic heart disease seen in more than 90% of the cases

Its Most common in Developed countries e.g. USA

Its Uncommon in under developed countries e.g. Africa

factors that might reduce the risk of coronary atherosclerosis:

a) Regular exercise

b) High levels of high-density lipoprotein cholesterol

Pathogenesis:
Severe and chronic atherosclerosis that causes narrowing of the lumen of one or more coronary arteries is the fundamental disorder underlying ischemic heart disease. ***With a 75% or greater atherosclerotic reduction in the lumen of one or more major coronary arteries***, any augmented coronary blood flow that may occur as a result of compensatory coronary vasodilation is insufficient to meet even moderate increases in myocardial oxygen demand, ***giving rise to classic angina pectoris***. Hence, a fixed 75% or greater reduction in the lumen of the coronary artery is defined **as "critical stenosis."** The onset of symptoms and the prognosis of ischemic heart disease, however, depend not only on the extent and severity of fixed, chronic anatomic disease but also critically on dynamic changes in the morphology of the coronary plaque.

These include the following:

- Acute plaque changes
- Coronary artery thrombosis
- Coronary artery vasospasm

Plaque:

A deposit , Consists of a fatty core and a fibrous Collagen cap, Develops in the inner wall of an artery in atherosclerosis.

1- **Acute Plaque Changes:**

Occur in Moderate stenosis 50-75%, but NOT in Critical Stenosis >75%

In the Acute Coronary syndromes , Precipitated by abrupt changes in plaque followed by thrombosis.

In the Chronic Atherosclerotic Plaques include:

A- Fissuring

B- Hemorrhage into the plaque

C- Plaque Rupture & Embolization into distal coronary vessels

Local disruption of plaque , increases risk of platelet aggregation + Thrombosis , Causing enlargement of the plaque.

Disrupted plaques are eccentric, with a soft core of necrotic debris. These plaques are rich in T-Cells and Macrophages.

T-Cells Activate Macrophages by interferon Gamma secretion.

Macrophages secrete Metaloproteins to help degrade the collagen Cap.

Plaque Rupture most dramatic Manifestation is acute coronary syndromes.

2- **Coronary Artery thrombosis:**

Plaque rupture exposes thrombogenic lipids and subendothelial collagen, thus initiating a wave of platelet aggregation, thrombin generation, and, ultimately, thrombus formation.

- If the vessel is **completely occluded** by the thrombus overlying the ruptured plaque, **acute MI occurs.**
- if the vessel obstruction by the thrombus is **incomplete**, unstable angina or a lethal arrhythmia occur, giving rise to **sudden cardiac death.**
- The **nonocclusive mural thrombus can also embolize small fragments** in the distal branches of the coronary artery. This may give rise to **microinfarcts**, found in patients who have had unstable angina.

3- Coronary Artery Vasospasm:

Usually ***occurs in Patients with pre-existing atherosclerosis***.

Maybe Induced by release of Vasospastic mediators like :

a- **Thromboxane A2** from platelet aggregation

b- **Reduced release of Endothelial cell derived relaxing factor** , due to Endothelial cell dysfunction.

c- Increased Adrenergic activity.

d- Smoking

Other Pathologic processes:

Uncommon causes to cause Ischemic heart disease:

- Emboli from Vegetations
- Severe Systemic Hypotension → Decreased coronary flow → Myocardial Ischemia
- Increased Myocardial O2 demand, due to left ventricular Myocardial Hypertrophy

Angina Pectoris

Definition:

Chest pain , Caused by transient reversible myocardial ischemia.

Three types:

1- Stable “typical”

2- Prinzmetal “Variant”

3- Unstable “Crescendo or preinfarction Angina”

More than one type can be seen in a given patient

Stable Angina:

- Chest pain with exertion or other form of stress , pain is described as crushing substernal sensation which may radiate down left arm.
- Associated with fixed narrowing 75% or more of one or more coronary arteries.
- O2 is adequate in basal conditions , but not adequate during exercise or any condition that stress the heart.
- Relieved by rest or Nitroglycerin which is a Vasodilator which decrease venous blood to the heart.

Prinzmetal Angina:

- Occurs at Rest , May wake patient from sleep.
- ***Associated with coronary artery spasm***
- Vasospasm Occurs near the atherosclerotic plaque , not at the site of plaque rupture

Unstable Angina:

- Characterized by increased frequency of anginal pain , induced by acute plaque changes with thrombosis , distal embolization of thrombus & Vasospasm.
- They are more intense and last longer than stable angina , less exertion is needed to cause it.
- May mean Irreversible myocardial ischemia, thus referred to as preinfarction angina.

Myocardial Infarction

Definition:

Myocardial necrosis caused by local ischemia.

Acute MI also known as Heart attack is the most common cause of death in developed countries.

Risk of MI increases between ages 45 & 54 , Men are 4 to 5 times more likely to develop MI. But after 80 both men and women have equal chances of MI.

Risk factors for MI are the same as for Coronary Atherosclerosis.

Pathogenesis.:

- ***most acute MIs are caused by coronary artery thrombosis***.
- Disruption of a plaque serves as the point for the generation of the thrombus. Vasospasm and platelet aggregation may contribute to occlusion, but they are rare.
- in the case of infarcts limited to the subendocardial myocardium, thrombi may be absent.
- In most such cases there is diffuse, stenosing coronary atherosclerosis but neither plaque disruption nor thrombosis. In such cases, **hypoperfusion of coronary vessels compromised by atherosclerosis is presumably sufficient to cause necrosis of subendocardial myocytes**

Myocardial necrosis begins within 20 to 30 minutes of the coronary artery occlusion.

The Endocardial region of the Myocardium is vulnerable to ischemic injury because:

1- Most poorly perfused region of the ventricular wall

2- Last area to receive blood from branches of epicardial coronary artery

3- High Intramural pressure compromising blood inflow

Because of all of the previous , MI typically begins in subendocardial region

Within few hours the zone of necrosis extends externally to involve mid and supepicardial areas of Myocardium.

Infarcts reach its full size in 3-6 hours

During this period , we can limit the size of Infarct by administering thrombolytic agents , e.g. Strptokinase or Tissue palsminogen activators

Cell death moves from subendocardium to involve entire thickness of ventricle.

Patchy Nontransmural Infarction occurs if occlusive thrombus is lysed by thrombolytic agents or by angioplasty before necrosis extends to entire ventricle thickness.

Location of MI is determined by:

a-Site of Vascular occlusion

b-Anatomy of coronary circulation

Site of Occlusion:

1- Occlusion in left anterior descending Coronary artery leads to anteroapical MI , which is an infarct in the anterior + apical areas of left ventricle.

2- Occlusion in right Coronary artery leads to infarcts involving posterior and basal portions of left ventricle.

Anatomy of Circulation:

A Person may have either right dominant , or left dominant circulation.

- Right dominant means Posterior ventricle supplied by right coronary artery
- Left dominant means Posterior ventricle supplied by Left coronary artery

Size of Infarct is influenced by several factors:

- Occlusion in proximal segments of Coronary → Large Infarct
- Occlusion in distal segments of coronary → Small infarcts

Extent of Infarct depends on Collateral circulation , which may limit size of infarct specially in epicardial regions .

Clinical Features of MI:

- Onset is accompanied my severe crushing substernal pain which may radiate to neck , jaws , left arm & epigastrium.
- In 50% of cases , preceded with Angina pectoris
- In contrast to Angina pectoris pain , MI pain lasts several hours to days and is NOT relieved by Nitroglycerin.
- Rapid weak Pulse
- Patients are Diaphoretic “sweaty”
- Dyspnea caused by impaired contractility of ischemic myocardium, with resultant pulmonary congestion and Edema.

Massive MIs involve 40% of left ventricle, Cardiogenic shock develops in 20 – 30% of patients with Massive MI

This MI doesn’t cause Pain so called Silent MI , its common in Elderly , DM , Hypertension patients.

ECG abnormalities like T wave inversion is important manifestation of MI

25% of patients with MI get sudden cardiac death caused by Lethal Arrhythmia which accounts to the vast majority of deaths occurring before hospitalization.

After reaching the Hospital : 10-20% have no complications , 80-90% develop one of:

A- Cardiac Arrhythmias 75-95%

B- Left ventricular failure with pulmonary edema 60%

C- Cardiogenic shock 10%

D- Rupture of free wall , septum or papillary muscle 4-8%

E- Thromboembolism 15-49%

MI Laboratory Diagnosis:

A number of enzymes and proteins are released by dying myocardial cells, so measurement of serum for concentration of these molecules are helpful.

1-Creatine Kinase 2-Troponins 3-Lactate dehydrogenase

Creatine kinase (CK):

An enzyme highly concentrated in the brain , Myocardium & skeletal muscle, composed of two dimmers M & B.

CK-MM is in Skeletal muscle + heart.

CK-BB is in brain , lungs & other tissues.

CK-MB is MAINLY from the Myocardium, but also in small amounts in skeletal muscle.

Total CK rises 2-4 Hours after MI , peaks at 24 hours , returns to normal at 72 hours.

Total CK is NOT specific for MI , because it may be elevated in other conditions like Skeletal muscle injury.

Specificity is enhanced by measuring CK-MB.

Total CK-MB rises 2-4 hours after MI , Peaks at 18 hours , Disappears in 48 hours.

CK index is a calculated value of CK-MB related to total CK , Helps in MI diagnosis.

If there is no increase in CK & CK-MB during 1st 2 days after chest pain , MI diagnosis is Excluded.

Troponins:

A group of proteins found in both cardiac and skeletal muscles. By use of immunologic essays it was discovered that there is:

1- Cardiac troponin T CTnt

2- Cardiac troponin 1 CTn1

CTn1 is more specific than CK-MB , because its only found in heart muscle , Unlike CK-MB which could be found in heart + skeletal. So **CTn1 is a reliable marker for Myocardial necrosis. Tropnin levels stay elevated for 4 to 7 days after MI which is a long period when compared to CK.**

Chronic Ischemic Heart disease, also known as Ischmic cardiomyopathy**.**

Definition:

Development of progressive congestive heart failure as a consequence of long term ischemic myocardial injury.

Clinical features:

- ❖ Severe progressive heart failure
- ❖ Episodes of angina pectoris or MI
- ❖ Arrhythmias with congestive heart failures

its difficult to distinguish between it and Dilated cardiomyopathy

Sudden Cardiac Death:

Can be caused by a variety of diseases:

1- Heart disease "most common cause"

2- Pulmonary embolisim

3- Ruptured aortic aneurysm

4- CNS disorders

5- Infection

S.C.D Accounts for 50% of all cardiovascular diseases.

Most common cause of S.C.D is Ischemic heart disease.

Chronic ischemia in Myocardium → ventricular fibrillation which is the most common cause of sudden cardiac death that is caused by Ischemic heart disease.

Unfortunately , sudden cardiac death is the initial manifestation in 50% of ischemic heart disease.

Morphology of Ischemic heart diseases:

Table 11-1. SEQUENCE OF CHANGES IN MYOCARDIAL INFARCTION

Time	Gross	Light Microscope	Electron Microscope	Other
0-30 min	No change	No change	*Reversible* changes (mitochondrial swelling, relaxation of myofibrils)	Loss of enzyme activity; glycogen loss
1-2 hr	No change	Few "wavy" fibers at margin of infarct	*Irreversible* changes (sarcolemmal disruption, electron-dense mitochondrial deposits)	
4-12 hr	No change	Early coagulation necrosis; edema; occasional neutrophils; minimal hemorrhage		
18-24 hr	Slight pallor or mottling	Continuing coagulation necrosis (nuclear pyknosis and disintegration; cytoplasmic eosinophilia); "contraction band" necrosis at periphery of infarct; neutrophilic infiltrate		
24-72 hr	Pallor	Complete coagulation necrosis of myofibers; heavy neutrophilic infiltrate with early fragmentation of neutrophil nuclei		
4-7 days	Central pallor with hyperemic border	Macrophages appear; early disintegration and phagocytosis of necrotic fibers; granulation tissue visible at edge of infarct		
10 days	Maximally yellow, soft, shrunken; purple border	Well-developed phagocytosis; prominent granulation tissue in peripheral areas of infarct		
7-8 wk	Firm, gray	Fibrosis		

Several important complications may be encountered in patients who have suffered myocardial infarcts, particularly if they are **transmural.** These occur at different times during the evolution of the infarct and can be summarized as follows:

- **Papillary muscle dysfunction**
- **External rupture of the infarct**
- **Mural thrombi**
- Clinically apparent **acute pericarditis** occurs in up to 15% of patients with MI within 2 to 4 days after the development of a transmural infarct. It may cause a significant pericardial effusion.
- **Ventricular aneurysms** are a late complication of large transmural MIs

Morphology of chronic ischemic heart disease:

The coronary arteries invariably contain areas of **moderate to severe atherosclerosis.** The heart is **enlarged,** sometimes to a striking degree, secondary to **dilation of all cardiac chambers.** Multiple areas of **myocardial fibrosis,** often including foci of transmural scarring, are usually present. A moderate degree of **hypertrophy** of the remaining myocardium is common. Despite the hypertrophy, however, wall thickness may be normal because of concomitant dilation. The endocardium is thick and opaque, and thrombi in varying stages of organization may be adherent to the endocardial surface. Microscopy reveals extensive myocardial fibrosis, owing to chronic ischemia. Among the remaining myocytes, both atrophic and hypertrophic fibers are present. Vacuolation of the sarcoplasm of some myofibers

Morphology of Sudden cardiac death:

The most common cardiac lesions in sudden death are those of coronary atherosclerosis and its complications. In most cases the degree of atherosclerosis is marked, with more than 75% reduction in the cross-sectional area of two or more vessels. The proximate cause of sudden cardiac death is not entirely clear in many cases. A number of studies suggest that acute plaque rupture, followed by coronary thrombosis and possibly vasospasm, triggers fatal ventricular arrhythmias. However, occlusive thrombi are absent in over 80% of cases of sudden cardiac death. In such cases, death is attributed to fatal arrhythmia. Morphologic manifestations of ischemic heart disease, such as recent or remote MIs, patchy myocardial fibrosis, wavy fiber change, or contraction band necrosis, are usually present. Other structural cardiac abnormalities have also been associated with sudden death and should be carefully sought in cases of sudden death associated with minimal atherosclerosis. These changes include various primary myocardial disorders (discussed later), conduction system abnormalities, and developmental abnormalities of the coronary arteries.

Table 11-2. CARDIAC CAUSES OF SUDDEN DEATH

Coronary Artery Diseases
Coronary atherosclerosis
Developmental abnormalities (anomalous origin, hypoplasia)
Coronary artery embolism
Other (vasculitis, dissection)
Myocardial Diseases
Cardiomyopathies
Myocarditis and other infiltrative processes
Right ventricular dysplasia
Valvular Diseases
Mitral valve prolapse
Aortic stenosis and other forms of left ventricular outflow obstruction
Endocarditis
Conduction System Abnormalities

End of Ischemic Heart Diseases

Done by:

Dr. Divine.

Hypertension

Hypertension Definition: a sustained diastolic pressure more than 90 mm hg or a sustained systolic pressure in excess of 140 mm hg.

Hypertension: Types:

- ❖ Primary or essential hypertension(90-95%).
- ❖ Secondary hypertension(5-10%):

- ➢ Renal: Acute glomerulonephritis, chronic renal disease, renal artery stenosis, renal vasculitis, renin-producing tumors.
- ➢ Endocrine: Adrenocortical hyperfunction (Cushing's syndrome),oral contraceptives,
- ➢ Pheochromocytoma, acromegaly, myxedema, thyrotoxicosis (systolic).

- ➢ Vascular: coarctation of aorta, polyarteritis nodosa, aortic insufficiency (systolic).
- ➢ Neurogenic: Psychogenic, increased intracranial pressure, acute stress etc.

They could be either:

Benign:

- ❖ Modest level.
- ❖ Fairly stable over years to decades.
- ❖ Compatible with long life.

Malignant(5%):

- ❖ Rapidly rising blood pressure.
- ❖ Severe hypertension (diastolic>120)
- ❖ Renal failure.
- ❖ Retinal hemorrhages and exudates (w/wo papilledema).
- ❖ Leads to death in 1 or 2 years if untreated.

Pathogenesis of Hypertension

Blood pressure:
BP = Cardiac Output x Peripheral Resistance

Hypertension: Possible Factors:

- ❖ Genetic:
  - ✓ Twin studies.
  - ✓ Familial clustering.
  - ✓ Gene linkage studies (red in previous slide)
- ❖ Environmental:
  - ✓ Low incidence in native Chinese as compared to immigrants to US.
  - ✓ May include: stress, obesity, inactivity, and heavy consumption of salt.

Morphology of blood vessels in hypertension.

- Hyaline arteriolosclerosis:
  - ✓ Can also be seen in elderly without hypertension and in diabetic patients.
  - ✓ Leads to benign nephrosclerosis due to diffuse renal ischemia.
- Hyperplastic arteriolosclerosis:
  - ✓ Characteristic of malignant hypertension.
  - ✓ May be associated with necrotizing arteriolitis.

Morphology of heart in Hypertension

Clinically:

–Early: no symptoms (chest x-ray, echo-, electro-).

–Late: heart failure, symptoms and signs of ischemic heart disease.

Hypertensive heart disease

Inadequately controlled hypertension has serious effects on many organs.

Diagnosis is based on presence of left ventricular hypertrophy in an individual with a history of hypertension.

The stimulus for ventricular hypertrophy is sustained pressure load on the left ventricular myocardium.

Hypertrophy involves mechanical effects & growth factors , the same molecules that promote hypertrophy trigger production of gene products that lead to myocyte dysfunction leading to premature cell death.

Metabolic requirements of hypertrophic ventricles are greater than normal ventricles and the ability of the heart to meet these demands decreases.

Clinical features:

In early stages , No symptoms. In these patients diagnosis is by detection of left ventricular hypertrophy by chest radiographs or echocardiograms

As left ventricle begins to fail , clinical manifestations of heart failure occur.
Heart failure + Hypertension = Poor Prognosis

Angina pectoris occurs , renal damage or cerebrovascular accidents occur contributing to morbidity and mortality. Risk for sudden cardiac death increases.

Effective control of Hypertension can prevent or lead to regression of hypertrophy and its associated risks.

Cor Pulmonale

Also known as Pulmonary heart disease

Definition:

Disease of right sided cardiac chambers caused by pulmonary hypertension resulting from pulmonary parenchymal or pulmonary vascular disease.

Pulmonary hypertension caused by left ventricular failure or a disease from left side is NOT cor pulmonale.

It may be Acute or Chronic

Major causes of cor pulmonale are

Table 11-3. DISORDERS THAT PREDISPOSE TO COR PULMONAL

Diseases of the Lungs
Chronic obstructive lung disease
Diffuse pulmonary interstitial fibrosis
Extensive, persistent atelectasis
Cystic fibrosis
Diseases of Pulmonary Vessels
Pulmonary embolism
Primary pulmonary vascular sclerosis
Extensive pulmonary arteritis (e.g., Wegener granulomatosis)
Drug-, toxin-, or radiation-induced vascular sclerosis
Disorders Affecting Chest Movement
Kyphoscoliosis
Marked obesity (pickwickian syndrome)
Neuromuscular diseases
Disorders Inducing Pulmonary Arteriolar Constriction
Metabolic acidosis
Hypoxemia
Chronic altitude sickness
Obstruction to major airways
Idiopathic alveolar hypoventilation

Common Causes are: Pulmonary Emboli , Chronic obstructive or restrictive lung disease , pulmonary vascular disease.

Acute cor Pulmonale:

- Often caused by Pulmonary embolism → Obstructing more than 50% of pulmonary vessels → Increasing burden on right side of the heart → Right heart failure
- In Acute cor pulmonale , Right ventricle is not Hypertrophied

Chronic Cor Pulmonale:

- Most common cause is chronic obstructive lung disease , or any of the diseases in table 11-3.
- Right ventricle is hypertrophied because it is Chronic.

Most patients with cor pulmonale are at increased risk for ventricular Arrhythmias.

Morphology of cor pulmonale:

In isolated **acute cor pulmonale,** the right ventricle is usually dilated. However, if sudden death occurs, for example, after massive pulmonary embolism, the heart may be of normal size. **Chronic cor pulmonale** is characterized by right ventricular, and often right atrial, hypertrophy. In extreme cases, the thickness of the right ventricular wall may exceed that of the left ventricle. When ventricular failure develops, the right ventricle and atrium may also be dilated. Such dilation may mask right ventricular hypertrophy. Because chronic cor pulmonale occurs in the setting of chronically elevated pulmonary arterial pressure, the pulmonary arteries often contain atheromatous plaques and other lesions of pulmonary hypertension.

The End of Hypertensive heart disease

Done by:

Dr. Divine , Used some of Dr.Sophias lecture also.

Rheumatic Fever and Heart Disease

***Rheumatic fever**: is an acute, immunologically mediated, multisystem inflammatory disease.*

follows an episode of group A streptococcal pharyngitis after an interval of a few weeks. pharyngitis may sometimes be almost asymptomatic .

caused by : the presence of a well-developed, highly antigenic capsule of group A streptococci .

The incidence and mortality rate of rheumatic fever have declined remarkably , due to :

1. improved socioeconomic conditions .
2. rapid diagnosis and treatment of streptococcal pharyngitis .
3. and an unexplained decrease in the virulence of group A streptococci .

Rheumatic fever may :

1. cause heart disease during its acute phase *(acute rheumatic carditis)*
2. or it may cause *chronic valvular deformities* that may not manifest themselves until many years after the acute disease.

- ✓ Fortunately, **rheumatic fever occurs in only about 3% of patients with group A streptococcal pharyngitis**.
- ✓ after an initial attack, there is increased vulnerability to reactivation of the disease with subsequent pharyngeal infections.
- ✓ It is strongly suspected that *acute rheumatic fever is a hypersensitivity reaction induced by group A streptococci*.
- ✓ It is proposed that antibodies directed against the M proteins of group A streptococci cross-react with normal proteins present in the **heart**, **joints**, and other tissues.
- ✓ **The fact that symptoms typically do not develop until 2 to 3 weeks after infection and that streptococci are absent from the lesions supports the concept that rheumatic fever results from an immune response against the offending bacteria**.
- ✓ streptococcal infection evokes an autoimmune response against self-antigens.

MORPHOLOGY :

In **acute rheumatic fever,** inflammatory infiltrates occur in **synovium, joints, skin,** and **heart.**

initial tissue reaction : focal fibrinoid necrosis

This provokes a mixed inflammatory response, which may take the form of either:

1. diffuse cellular infiltrate.
2. localized aggregation of cells that resembles a granuloma.

- ✓ **Fibrosis is common in cardiac tissues**
- ✓ it is responsible for the valvular deformities in chronic rheumatic heart disease.
- ✓ **Acute rheumatic carditis** is pancarditis , i.e : characterized by inflammatory changes in all three layers of the heart.
- ✓ The multiple foci of inflammation within the connective tissues of the heart (called **Aschoff bodies) is** The hallmark of acute rheumatic carditis.

The Aschoff bodies contain a central focus of fibrinoid necrosis surrounded by :

1. a chronic mononuclear inflammatory infiltrate
2. occasional large macrophages with vesicular nuclei
3. abundant basophilic cytoplasm, called **Anitschkow cells.**

- ✓ In the myocardium , the Aschoff bodies often lie in close proximity to a small vessel and may encroach on its wall.
- ✓ Myocardium also contain diffuse interstitial inflammatory infiltrates.
- ✓ In severe cases, myocarditis impair myocardial function to cause generalized dilation of the chambers.

Pericardial involvement is manifested :

1. grossly
2. microscopically
   - ✓ by the presence of **fibrinous pericarditis,** sometimes associated with a serous or serosanguineous pericardial effusion.
   - ✓ Involvement of **endocardium** is common . it may affect any valve.
   - ✓ The valvular inflammation is mostly in the mitral and aortic valves.
   - ✓ affected valves are : **edematous , thickened ,** and **show foci of fibrinoid necrosis**
   - ✓ The acute changes may resolve without sequelae or may progress .

Changes in other organs (**arthritis of the large joints),** characterized by :

1. chronic inflammatory infiltrates
2. edema

- in the : 1- involved joints 2- periarticular soft tissues.
- **It's self-limited and does not cause chronic deformity**
- **Pulmonary involvement is uncommon , which us manifested by : 1-** chronic interstitial inflammatory infiltrates -2- fibrinous inflammation of pleural surface
- **Skin changes** take the form of :

1. **subcutaneous nodules** : contain focal lesions (large Aschoff bodies)
2. or **erythema marginatum :** presents as a maculopapular rash

Chronic rheumatic heart disease : irreversible deformity of cardiac valves , from previous episodes of acute valvulitis.

mitral valve is abnormal in approximately 95% , and combined aortic and mitral valve disease is present in about 25% of patients.

Right-sided valvular disease is uncommon

Scarring of the valve leaflets cause reduction in the diameter of the orifice **(stenosis),** or prevent proper closure of the valve leaflets, resulting in **regurgitation** of blood during diastole

Sometimes stenosis and regurgitation coexist, (one defect predominates)
stenosis and regurgitation increase demands on myocardium because of increased pressure load.

if severe enough, causes **cardiac failure** .

Chronic rheumatic mitral valvulitis causes stenosis(more frequently in females)
In **mitral stenosis,** the valve leaflets and chordae tendineae are 1- thick, 2- rigid, and 3- interadherent

The valve is narrowed to a slitlike channel, "fish-mouth" deformity

The left atrium is **dilated** and **hypertrophied**, the endocardial surface is **thickened**(above the posterior mitral leaflet)

lungs are **firm** and **heavy** as a result of chronic passive congestion.

in long-standing cases , right ventricle and atrium are dilated and hypertrophied .

In **mitral regurgitation,** deformed mitral leaflets are retracted, causes left ventricular dilation and hypertrophy.

Chronic aortic valvulitis (more often in males) is associated with elements of mitral valvulitis.

In **aortic stenosis,** valve cusps are **thickened, firm, and adherent**.

resultant aortic valve orifice is rigid, triangular channel
It places a load on the left ventricle, which undergoes concentric hypertrophy.
left ventricular failure is associated with dilation of the chamber and congestive heart failure.
Fibrosis of the valve leaflets may also cause them to retract toward the aortic wall, resulting in **aortic regurgitation,** left ventricular hypertrophy, and dilation.

Clinical Features :

- *Acute rheumatic fever* occurs anywhere from 10 days to 6 weeks after an episode of pharyngitis caused by group A streptococci.
- genetic susceptibility that regulates the hypersensitivity reaction is suspected.
- The peak incidence is between the ages of 5 and 15
- pharyngeal cultures for streptococci are **negative** by the time the illness begins
- antibodies to one or more streptococcal enzymes are present in the sera of most patients.
- The predominant clinical manifestations of acute rheumatic fever are :

1. arthritis : which is much more common in adults than in children, preferentially occurs in larger joints and tends to involve different joints sequentially

2. carditis : include pericardial friction rubs, weak heart sounds tachycardia, and other arrhythmias , In severe cases, myocarditis may cause overt congestive heart failure

- left ventricular dilatation causes the papillary muscles to pull on the chordae tendineae of the mitral valve cusps
- resulting , in the development of functional, potentially reversible mitral insufficiency
- *Chronic rheumatic carditis* usually does not cause clinical manifestations for years or even decades .
- signs and symptoms of valvular disease depend on which cardiac valve or valves are involved.
- patients with chronic rheumatic heart disease may suffer from arrhythmias

Timely surgical replacement of diseased valves has greatly improved the outlook for patients with chronic rheumatic heart disease.

End of Rheumatic fever

Done By:

Dr. Aoks

PERICARDIAL DISEASES

Diseases of the pericardium include inflammatory conditions and effusions. These are most frequently noted in conjunction with local myocardial or mediastinal diseases and in patients with certain systemic conditions, such as uremia.

- **Pericarditis**

Primary pericarditis is ***uncommon*** and usually ***infectious*** in origin.
It is caused by :

- ✓ Viruses infections (the most common cause)
- ✓ Pyogenic bacteria
- ✓ Mycobacteria
- ✓ Fungi

An accompanying myocarditis may be present, *particularly in the case of viral infections*. More often the pericarditis is secondary to acute MI, cardiac surgery, or radiation to the mediastinum. ***Uremia*** is probably the most common systemic disorder associated with pericarditis. Less common secondary causes include rheumatic fever, systemic lupus erythematosus, and metastatic malignancies. The latter are usually associated with a bloody effusion.

Pericarditis may :

- ✓ cause immediate hemodynamic complications if a significant effusion is present.
- ✓ resolve without significant sequelae.
- ✓ progress to a chronic fibrosing process.

MORPHOLOGY

- ❖ The appearance of acute pericarditis **varies** with its cause.
- ❖ In patients with uremia or acute rheumatic fever, the exudate is typically **fibrinous** and imparts a ***shaggy***, irregular appearance to the pericardial surface (" bread and butter " pericarditis).
- ❖ A fibrinous exudate may also be seen in cases of viral pericarditis.
- ❖ In acute bacterial pericarditis the pericardial exudate is fibrinopurulent, while in tuberculosis the pericardium contains caseous material.
- ❖ Pericardial metastases are visible grossly as irregular nodular excrescences, often with a ***shaggy*** fibrinous exudate and a bloody effusion.
- ❖ In most cases, acute fibrinous or fibrinopurulent pericarditis resolves without any sequelae. However, when there is extensive suppuration or caseation, healing gives rise to chronic pericarditis.

- ❖ The appearance of **chronic pericarditis** ranges from delicate adhesions to dense, fibrotic scars that obliterate the pericardial space.
- ❖ In extreme cases the heart is so completely encased by dense scar tissue that it cannot expand normally during diastole, a condition called **constrictive pericarditis**

Q: what is constrictive pericarditis ? Q : whats the common cause for pericarditis ?

Q: what the most common systemic cause? Q: where can we find shaggy appearance?

Clinical Features

The manifestations of pericarditis include atypical chest pain, which is often worse on reclining, and a high-pitched friction rub. When associated with significant exudate in the pericardial sac, acute pericarditis may cause signs and symptoms of cardiac tamponade, which include faint distant heart sounds, distended neck veins, declining cardiac output, and shock. Chronic constrictive pericarditis produces a combination of venous distention and low cardiac output, which may be difficult to distinguish from restrictive cardiomyopathy, as noted previously.

- **Pericardial Effusions**

Processes besides inflammation may cause fluid to accumulate in the pericardial space. The nature of the fluid **varies** with the cause of the effusion. The major types of pericardial effusion and some of their more common causes are listed as follows:

- ***Serous****:* congestive heart failure, hypoalbuminemia of any cause
- ***Serosanguineous****:* blunt chest trauma, malignancy
- ***Chylous****:* mediastinal lymphatic obstruction

Pericardial effusions are often **symptomatic**. Surprisingly large volumes of fluid can be accommodated if the accumulation occurs slowly. Massive or rapidly developing effusions may cause cardiac tamponade.

The normally smooth, glistening pericardial surface is covered by ***shaggy*** fibrinous exudate. In this case, the pericarditis developed because of uremia and caused a fatal cardiac tamponade.

Hemopericardium, more properly considered separately from hemorrhagic pericardial effusions, indicates the presence of pure (undiluted) blood in the pericardial sac. Important causes include ruptured aortic aneurysms, ruptured myocardial infarcts, and penetrating traumatic injury to the heart. The escaping blood rapidly fills the pericardial space and leads to cardiac tamponade and death.

Nonbacterial Thrombotic Endocarditis

*Non**B**acterial **T**hrombotic **E**ndocarditis* (NBTE) is characterized by the deposition of small masses of fibrin, platelets, and other blood components on the leaflets of the cardiac valves. **In contrast to the vegetations of infective endocarditis**, discussed in the next section, the valvular lesions of NBTE are ***sterile*** and ***do not contain microorganisms***. Valvular damage is not a prerequisite for NBTE. Indeed, the condition is *usually found on previously normal valves*. The pathogenesis of NBTE is incompletely understood; it is thought that subtle endothelial abnormalities and hypercoagulable states predispose to its development. Malignancies, particularly adenocarcinomas, have been identified in up to 50% of patients with NBTE. These patients may also exhibit other features of hypercoagulability, such as deep venous thrombosis. Although NBTE may occur in otherwise healthy individuals, a wide variety of diseases associated with general debility or wasting are associated with an increased risk of NBTE. The term *marantic endocarditis* has also been used to describe this entity, in recognition of the increased frequency of NBTE in cachectic patients.

MORPHOLOGY

Grossly, NBTE is characterized by the presence of multiple small nodules along the lines of valve closure, similar to the valvular lesions of acute rheumatic fever. The nodules usually measure less than 5 mm in diameter but may become fairly large and friable. The valve leaflets appear normal on gross inspection. Although any valve may be affected, the mitral valve is the most common site, followed by the aortic valve. Microscopically, the nodules are composed of eosinophilic material (fibrin) and a delicate layer of aggregated platelets. The underlying valve is typically free of inflammation or fibrosis, in contrast to the valves in acute rheumatic fever. The lesions of NBTE often resolve spontaneously, leaving in their wake delicate strands of fibrous tissue termed **Lambl excrescences.**

Clinical Features

Is usually asymptomatic. Sometimes, particularly in patients with larger lesions, fragments of the vegetations may embolize and cause infarcts in the brain and other organs. The lesions of NBTE also serve as a potential nidus for bacterial colonization and thus may be complicated by the development of infective endocarditis.

- **Libman-Sacks Endocarditis**

The term *Libman-Sacks endocarditis* refers to sterile vegetations that may develop on the cardiac valves of patients with systemic lupus erythematosus. These lesions occur most frequently on the ventricular surfaces of the mitral and tricuspid valves but can also involve other endocardial surfaces. In contrast to the lesions of typical NBTE (discussed earlier), the small vegetations of Libman-Sacks endocarditis have no special predilection for the lines of valve closure. With increasing use of steroids for treatment of lupus, these lesions have become quite uncommon.

- **Infective Endocarditis**

The term *infective endocarditis* designates infection of the cardiac valves or mural surface of the endocardium, resulting in the formation of an adherent, bulky mass of thrombotic debris and organisms, termed a *vegetation*. Virtually any type of microorganism is capable of causing endocarditis, although most cases are caused by bacteria.

Infective endocarditis has traditionally been subdivided into acute and subacute forms. Cases of *acute endocarditis* are classically associated with infection of the valves by organisms of high virulence, such as *Staphylococcus aureus*. Such organisms are capable of infecting even structurally normal valves and cause rapidly progressive infection, with little accompanying local host reaction. *Subacute endocarditis*, in contrast, is typically associated with infection of previously abnormal valves by organisms of lower virulence, such as α-hemolytic streptococci. The resultant infections tend to progress somewhat more slowly and are often accompanied by the development of a local inflammatory reaction and granulation tissue in the affected valve. In the era of antibiotics, however, therapy often modifies the morphology and clinical progression of disease, thus blurring the distinction between acute and subacute cases.

Etiology and Pathogenesis

Infection occurs when organisms are implanted on the endocardial surface during episodes of bacteremia. In some instances the cause of the hematogenous infection is obvious, as in the case of intravenous drug abusers who inject contaminated material directly into the bloodstream; an infection elsewhere or a previous dental, surgical, or other interventional procedure (e.g., urinary catheterization) may also seed the bloodstream. In other cases, however, the source of bacteremia is occult and presumably related to trivial injuries to the skin or mucosal surfaces, as may be encountered, for example, during brushing the teeth.

In some cases, the initial valvular change is that of endothelial injury followed by the development of a localized fibrin-platelet aggregate (see NBTE, discussed earlier). These foci may then serve as attachment sites for circulating microorganisms. In other instances, bacteria may adhere directly to the valve surface in the absence of a preexisting focus of NBTE.

Conditions that increase the risk of infective endocarditis can be segregated into three categories:

(1) preexisting cardiac abnormalities,
(2) prosthetic heart valves,
(3) intravenous drug abuse.

- A number of cardiac abnormalities predispose individuals , infective endocarditis. The risk of endocarditis is increased by any condition that causes increased hemodynamic trauma to the endocardial surface, such as high pressure shunts within the heart (e.g., small ventricular septal defects) or chronic valvular diseases (e.g., chronic rheumatic heart disease, degenerative calcific aortic stenosis, mitral valve prolapse). Because of its high prevalence, mitral valve prolapse has emerged as the most common predisposing factor for infective endocarditis.
- With an increasing number of patients undergoing valve replacement surgery, prosthetic valves now account for 10% to 20% of cases of infective endocarditis. There is no difference in the incidence of endocarditis between mechanical and bioprosthetic valves. The frequency of endocarditis is also increased, as might be expected, in individuals with indwelling intravascular catheters.
- Intravenous drug abusers are at a high risk for development of infective endocarditis. In this setting, infective endocarditis usually occurs on previously normal valves, often involving the cardiac valves on the right side of the heart.

The causative organisms differ somewhat in the three high-risk groups. Endocarditis of native (not prosthetic) valves is caused most commonly (50% to 60% of cases) by α-hemolytic (viridans) streptococci, which usually attack previously damaged valves. The more virulent ***S. aureus*** organisms attack healthy or deformed valves and are responsible for 10% to 20% of cases. The roster of the remaining bacteria includes enterococci and the so-called HACEK group (***Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella***), all commensals in the oral cavity. Prosthetic valve endocarditis is caused most commonly by coagulase-negative staphylococci (e.g., *S.* ***epidermidis***). Other agents include gram-negative bacilli and fungi. In intravenous drug abusers, ***S. aureus***, commonly found on the skin, is the major offender; other, less frequent, causes in this population of patients include streptococci, gram-negative rods, and fungi.

Infective endocarditis is a particularly difficult infection to eradicate because of the avascular nature of the heart valves. In view of the paucity of blood vessels, the inflammatory response to the infection is relatively scant, if present at all. Thus, even avirulent organisms can proliferate in an uncontrolled fashion. Before effective antibiotics were available, infective endocarditis was almost always fatal.

Morphology

The hallmark of infective endocarditis is the presence of valvular vegetations containing bacteria or other organisms. The aortic and mitral valves are the most common sites of infection, although the valves of the right side of the heart may also be involved, particularly in cases of endocarditis occurring in intravenous drug abusers. The vegetations may be single or multiple and may involve more than one valve. The appearance of the vegetations is influenced by the type of organism responsible for the infection, the degree of host reaction to the infection, and previous antibiotic therapy. Fungal endocarditis, for example, tends to cause larger vegetations than does bacterial infection. Although highly virulent organisms tend to cause acute endocarditis, treatment with antibiotics may curb the infection sufficiently to change the morphology of the vegetations to a more subacute form.

The vegetations in cases of classic **acute endocarditis** begin as small excrescences, which may be grossly indistinguishable from those of NBTE, although they are more commonly solitary than the vegetations in the latter condition. As the organisms proliferate, the vegetations enlarge progressively and eventually form bulky, friable lesions that may obstruct the valve orifice. The vegetations may cause rapid destruction of the valves, often resulting in rupture of the leaflets, chordae tendineae, or papillary muscles. The infection may eventually extend through the valve into the adjacent myocardium to produce abscesses in the perivalvular tissue known as **ring abscesses**. Microscopic examination of the vegetations reveals large numbers of organisms admixed with fibrin and blood cells. When confined to the valve, the vegetations elicit minimal inflammatory response. A brisk neutrophilic inflammatory response occurs once the infection extends beyond the avascular valves. **Systemic emboli** may occur at any time because of the friable nature of the vegetations, and they may cause infarcts in the brain, kidneys, myocardium, and other tissues. Because the embolic fragments contain large numbers of virulent organisms, **abscesses often develop at the sites of such emboli**.

The vegetations of **subacute endocarditis** tend to be somewhat firmer and are associated with less valvular destruction than those of acute endocarditis, although the distinction between the two forms may be difficult. Subacute infections are less likely to erode into the myocardium, and perivalvular abscesses are uncommon. Microscopically, the vegetations of typical subacute infective endocarditis are distinguished from those of acute disease by the presence of **granulation tissue** at their bases. With the passage of time, fibrosis, calcification, and a chronic inflammatory infiltrate may develop. **Systemic emboli** may also develop in subacute endocarditis. In contrast to those of acute endocarditis, however, **the resultant infarcts are less likely to undergo suppuration** because of the less virulent nature of the offending organisms.

Clinical Features

The onset of infective endocarditis may be gradual or explosive, depending on the organism responsible for the infection. Low-grade fever, malaise, and weight loss are characteristic of cases caused by organisms of low virulence, while more acute cases, in contrast, typically present as high fevers, shaking chills, and other evidence of overt septicemia. ***Changing cardiac murmurs*** are almost always present, although they may be difficult to detect early in the course of acute endocarditis. The *spleen is often enlarged*, and clubbing of the digits may be seen, particularly in subacute cases. *Systemic emboli* are very common in all forms of infective endocarditis, manifesting as neurologic deficits, retinal abnormalities, necrosis of the digits, and infarcts of the myocardium and other viscera. Pulmonary emboli may occur in patients with right-sided endocarditis and large vegetations on the tricuspid or pulmonic valves. Entrapment of infected emboli in the walls of blood vessels may cause local infection and weakening of the vessel wall, with the formation of so-called *mycotic* aneurysms. Petechiae (small hemorrhages) may be seen on the skin or mucosal surfaces. They may be caused by microemboli or deposition of immune complexes formed in response to chronic antigenemia. ***Renal lesions*** are common and include both renal infarcts and glomerulonephritis, the latter resulting from entrapment of immune complexes in the glomeruli. Over a period of days to months, progressive valvular destruction in untreated cases results in valvular regurgitation and congestive heart failure.

Repeated blood cultures are extremely important in the evaluation of patients with suspected infective endocarditis. Cultures for both aerobic and anaerobic organisms should be obtained the moment the possibility of endocarditis is considered. In a minority of cases of infective endocarditis, blood cultures remain negative because of either the fastidious nature of the organism or the effects of previous antibiotic therapy

Done by

Dr.Nono

VASCULITIS

Vasculitis, or inflammation of vessel walls, occurs in diverse clinical settings.

- Depending on the vascular bed affected (e.g., central nervous system vs. heart vs. small bowel), the manifestations can be protean. include constitutional signs and symptoms such as fever, myalgia, arthralgias, and malaise.

- Vessels of any type in virtually any organ can be affected, and most vasculitides can affect all small vessels from arterioles to capillary to venules.

    - ✓ several of the vasculitides tend to affect only vessels of particular caliber or tissue beds : the aorta and medium-sized arteries, others principally affect only smaller arterioles.

- ***The two most common pathogenic mechanisms of vasculitis are:***

1) immune-mediated inflammation
2) direct invasion of vascular walls by infectious pathogens.

✓ *infections can also indirectly induce a noninfectious vasculitis,* (by generating immune complexes or triggering cross-reactivity).

- In any given patient, it is critical to distinguish between infectious and immunologic mechanisms, because immunosuppressive therapy is used treatment the mmune-mediated vasculitis but could very well be counterproductive for infectious vasculitides.

- Physical and chemical injury, such as from irradiation, mechanical trauma, and toxins, can also cause vasculitis.

° ***There 20 primary forms of vasculitis are recognized, and classificaied according to:***

- ✓ vessel size
- ✓ role of immune complexes
- ✓ presence of specific autoantibodies
- ✓ granuloma formation
- ✓ organ tropism
- ✓ population demographics

Classification and Characteristics of Selected Immune-Mediated Vasculitides:

Vasculitis type*	Examples	Description
Large-Vessel Vasculitis (Aorta and Large Branches to Extremities, Head, and Neck)	**Giant-cell (temporal) arteritis**	Granulomatous inflammation; also frequently involves the temporal artery. Usually occurs in patients older than age 50 and is associated with polymyalgia rheumatica.
	Takayasu arteritis	Granulomatous inflammation usually occurring in patients younger than age 50
Medium-Vessel Vasculitis (Main Visceral Arteries and Their Branches)	**Polyarteritis nodosa**	Necrotizing inflammation typically involving renal arteries but sparing pulmonary vessels
	Kawasaki disease	Arteritis with mucocutaneous lymph node syndrome; usually occurs in children. Coronary arteries can be involved with aneurysm formation and/or thrombosis.
Small-Vessel Vasculitis (Arterioles, Venules, Capillaries, and Occasionally Small Arteries)	**Wegener granulomatosis**	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small vessels, including glomerulonephritis. Associated with c-ANCAs.
	Churg-Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small vessels. Associated with asthma and blood eosinophilia. Associated with p-ANCAs.
	Microscopic polyangiitis	Necrotizing small-vessel vasculitis with few or no immune deposits; necrotizing arteritis of small and medium-sized arteries can occur. Necrotizing glomerulonephritis and pulmonary capillaritis are common. Associated with p-ANCAs.

c-ANCAs, antineutrophil cytoplasmic antibodies, cytoplasmic localization

p-ANCAs, antineutrophil cytoplasmic antibodies, perinuclear localization.

Noninfectious Vasculitis

The main immunologic mechanisms that initiate noninfectious vasculitis are :

(1) immune complex deposition,

(2) antineutrophil cytoplasmic antibodies (ANCAs),

(3) anti-endothelial cell antibodies. (Kawasaki disease)

1) Immune Complex-Associated Vaculitis
Examples;

I. systemic lupus erythematosus (SLE)-associated vasculitis.
II. vasculitis associated with drug hypersensitivity (e.g. penicillin)
III. vasculitis associated secondarily with viral infections (e.g. hepatitis B infection)

2) Antineutrophil Cytoplasmic Antibodies

- circulating antibodies react with neutrophil cytoplasmic antigens, so-called *ANCAs.*
  - ✓ ANCAs are a heterogeneous group of autoantibodies directed against constituents (mainly enzymes) of neutrophil primary granules, monocyte lysosomes, and endothelial cells.

- ***There are Two types of ANCAs are recognized based on immunofluorescence staining patterns:***
  A. Cytoplasmic localization (c-ANCA), wherein the most common target antigen is proteinase-3 (PR3), a neutrophil granule constituent
  B. Perinuclear localization (p-ANCA), wherein most of the autoantibodies are specific for myeloperoxidase (MPO).

✓ *c-ANCA is typical of Wegener granulomatosis*
✓ *p-ANCA is found in most cases of microscopic polyangiitis and Churg-Strauss syndrome*.

- ANCAs levels can reflect the degree of inflammatory activity (quantitative diagnostic markers)

mechanism for ANCA vasculitis is:

- Neutrophil release of PR3 and MPO (e.g., in the setting of infections) incites ANCA formation in a susceptible host.
- Some underlying disorder (e.g., infection, endotoxin exposure, etc.) elicits inflammatory cytokines, such as TNF, that result in surface expression of PR3 and MPO on neutrophils and other cell types.
- ANCAs react with these cytokine-primed cells and either cause direct injury (e.g., to endothelium) or induce activation (e.g., in neutrophils).
- ANCA-activated neutrophils degranulate and also cause injury by the release of reactive oxygen species, engendering EC toxicity and other direct tissue injury.

ANCAs directed against constituents other than PR3 and MPO are also found in some patients with inflammatory disorders that do not involve vasculitis (e.g., inflammatory bowel disease, primary sclerosing cholangitis, and rheumatoid arthritis).

Polyarteritis Nodosa(PAN)

- is a systemic vasculitis of small or medium-sized muscular arteries (but not arterioles, capillaries, or venules).

✓ typically involving renal and visceral vessels but sparing the pulmonary vessels.

Morphology

- Classic PAN is characterized by segmental transmural necrotizing inflammation of **small to medium-sized arteries.**
- Vessels of the kidneys, heart, liver, and GI tract are involved in descending order of frequency.
- Lesions usually involve only **part of the vessel circumference,** with a predilection for branch points.
- The inflammatory process weakens the arterial wall and can lead to aneurysms or even rupture.
- Impaired perfusion with ulcerations, infarcts, ischemic atrophy, or hemorrhages in the distribution of affected vessels may be the first sign of disease.
- During the acute phase there is **transmural inflammation** of the arterial wall with a mixed infiltrate of neutrophils, eosinophils, and mononuclear cells, frequently accompanied by **fibrinoid necrosis**.
- Luminal thrombosis can occur. Later, the acute inflammatory infiltrate is replaced by fibrous (occasionally nodular) thickening of the vessel wall that can extend into the adventitia.
- Characteristically, all stages of activity (from early to late) may coexist in different vessels or even within the same vessel, suggesting ongoing and recurrent pathogenic insults.

Clinical Course

- PAN is a disease primarily of young adults, but it can occur at all ages.

- The course can vary from acute to chronic but is typically episodic, with long symptom-free intervals. Because the vascular involvement is widely scattered, the clinical findings may be varied and puzzling.

- If untreated, the disease is fatal in most cases.

- **manifestations are** :
  malaise, fever, weight loss; hypertension, usually developing rapidly; abdominal pain and melena (bloody stool) caused by vascular GI lesions;diffuse muscular aches and pains; and peripheral neuritis, predominantly affecting motor nerves.

- Renal (arterial) involvement is common and a major cause of death, although glomerular arteriolar involvement (and thus, glomerulonephritis) is absent.

- Biopsy is often necessary to confirm the diagnosis.

- There is no association with ANCA, but some 30% of patients with PAN have hepatitis B antigenemia.

- therapy with corticosteroids and cyclophosphamide results in remissions or cures in 90%.

Thromboangiitis Obliterans (Buerger Disease)

- *Thromboangiitis obliterans (Buerger disease)* is a distinctive disease that often leads to vascular insufficiency
- it is characterized by segmental, thrombosing acute and chronic inflammation of medium-sized and small arteries, principally the tibial and radial arteries, with occasional secondary extension into extremity veins and nerves.

Buerger disease is a condition that occurs almost exclusively in heavy smokers of cigarettes, usually beginning before age 35.

Pathogenesis

- The strong relationship to cigarette smoking is thought to involve direct toxicity to endothelium by some tobacco products, or an idiosyncratic immune response to the same agents.

- Most Buerger patients have hypersensitivity to intradermally injected tobacco extracts, and their vessels show impaired endothelium-dependent vasodilation when challenged with acetylcholine.

Genetic influences are suggested by an increased prevalence in certain ethnic groups (Israeli, Indian subcontinent, Japanese) and an association with certain MHC haplotypes

Aneurysms and dissection

An *aneurysm* is a *localized abnormal dilation of a blood vessel or the wall of the heart.*

- ***true aneurysm*** : *aneurysm* is involves all three arterial wall components (intima, media, & adventitia) or the attenuated wall of the heart.
  Examples:

  ✓ Atherosclerotic , syphilitic and congenital vascular aneurysms . and the left ventricular aneurysm that can follow a myocardial infarction.

- ***false aneurysm*** (also called *pseudoaneurysm*): is a breach in the vascular wall leading to an extravascular hematoma that freely communicates with the intravascular space ("pulsating hematoma").

  Examples:

  ✓ The most common false aneurysm is a post-myocardial infarction rupture that are contained by a pericardial adhesion.or a leak at the junction of a vascular graft with natural artery

- ***arterial dissection*** arises when blood enters the wall of the artery, as a hematoma dissecting **between its layers**. Dissections are often , but not always aneurysmal.

✓ Both true and false aneurysms, as well as dissections, can rupture, often with catastrophic consequences.

Aneurysms are Classified by macroscopic shape and size into :

1. *Saccular* aneurysms :

✓ spherical outpouchings (involving only one portion of the vessel wall)
✓ vary in size from 5 to 20 cm in diameter & often contain thrombi.
✓ Seen in syphilitic aneurysm

2. *Fusiform* aneurysms:

✓ diffuse, circumferential dilation of a long vascular segment;
✓ vary in diameter (≤20 cm) and in length
✓ involve extensive portions of the aortic arch, abdominal aorta, or even the iliacs.

Particular aspects of shape and size are not specific for any disease or clinical manifestations.

- *The two most important causes of <u>aortic aneurysms are atherosclerosis and cystic medial degeneration of the arterial media.</u>*

  Other causes that weaken vessel walls and lead to aneurysms include:

  - ✓ trauma, congenital defects (e.g., *berry* aneurysms), infections (*mycotic* aneurysms), syphilis. and vasculitis.

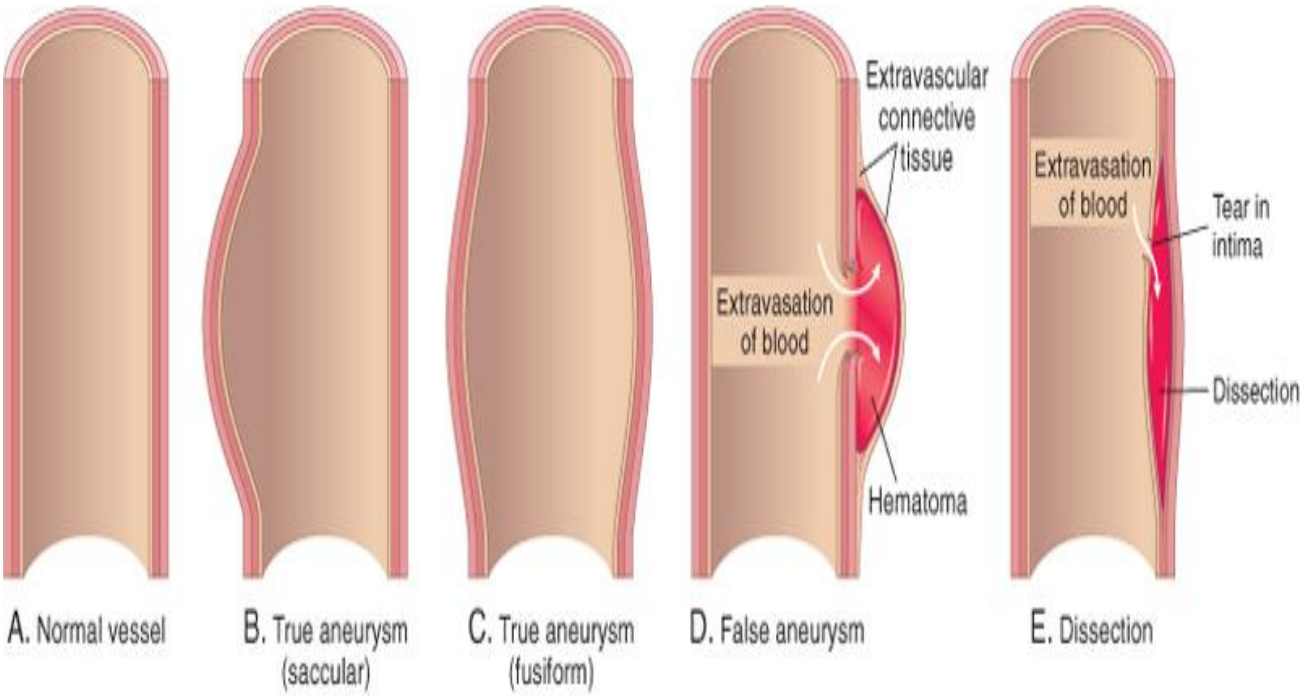
- Infection of a major artery that weakens its wall is called a *mycotic aneurysm;* thrombosis and rupture are possible complications.

- <u>Myctic aneurysms can originate :</u>

  (1) from embolization of a septic thrombus, usually as a complication of infective endocarditis

  (2) as an extension of an adjacent suppurative process

  (3) by circulating organisms directly infecting the arterial wall.



Abdominal Aortic Aneurysm

- Atherosclerosis, the most common cause of aneurysms, causes thinning and weakening of the media secondary to intimal plaques.

- plaques compress the underlying media and also compromise nutrient and waste diffusion from the vascular lumen into the arterial wall. The media consequently undergoes degeneration and necrosis, thus allowing the dilation of the vessel.

- *Atherosclerotic aneurysms occur most frequently in the abdominal aorta* (*abdominal aortic aneurysm*, often abbreviated AAA), but the common iliac arteries, the arch, and descending parts of the thoracic aorta can also be involved.

Pathogenesis

- AAA occurs more frequently in men and rarely develops before age 50.
- Atherosclerosis is a major cause of AAA

Others like : hypertension , hereditary defect fibrillin production in Marfan disease affecting elastic tissue synthesis.

- ***AAA can results from an altered balance of ECM proteins degradation and synthesis:***

I. *Matrix metalloproteinases (MMPs)* are expressed in aortic aneurysms at elevated levels compared with the normal vessel wall, and have the capacity to degrade virtually all components of the ECM in the arterial wall (collagens, elastin, proteoglycans, laminin, fibronectin).

II. decreased level of tissue inhibitor of *metalloproteinases (TIMP)* can also contribute to overall ECM degradation.

the production of T_H2 cytokines (e.g., IL-4 and IL-10) drive macrophages to produce increased amounts of elastolytic MMPs.

Morphology

- Usually positioned below the renal arteries and above the bifurcation of the aorta
- AAA can be saccular or fusiform, (15 - 25 cm in diameter)
- There is severe complicated atherosclerosis with destruction and thinning of the underlying aortic media; the aneurysm frequently contains a bland, laminated, poorly organized mural thrombus that may fill some or all of the dilated segment.
- Occasionally, the aneurysm can affect the renal and superior or inferior mesenteric arteries, either by producing direct pressure or by narrowing or occluding vessel ostia with mural thrombi. Not infrequently, AAA is accompanied by smaller aneurysms of the iliac arteries.

Two AAA variants merit special mention:

Inflammatory AAAs:

- characterized by dense periaortic fibrosis containing abundant lymphoplasmacytic infiltrate with many macrophages and often giant cells.

Mycotic AAAs

- are atherosclerotic lesions infected by lodging of 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.

Clinical Course

The clinical consequences of AAA include:

a. Rupture into the peritoneal cavity or retroperitoneal tissues with massive, potentially fatal hemorrhage

b. Obstruction of a branch vessel resulting in downstream tissue ischemic injury-for example, iliac (leg), renal (kidney), mesenteric (gastrointestinal [GI] tract), or vertebral (spinal cord) arteries

c. Embolism from atheroma or mural thrombusImpingement on an adjacent structure (e.g., compression of a ureter or erosion of vertebrae)

d. Presentation as an abdominal mass (often palpably pulsating) that simulates a tumor

Timely surgery is critical; operative mortality for unruptured aneurysms is approximately 5%, whereas emergency surgery after rupture carries a mortality rate of more than 50%.

- atherosclerosis is a systemic disease, a patient with an AAA is very likely to have atherosclerosis in other vascular beds (i.e.IHD and stroke)

Syphilitic Aneurysm

- The *obliterative endarteritis* (characteristic of the tertiary stage of syphilis (lues)) can involve small vessels in any part of the body.

- Involvement of the vasa vasorum of the aorta is particularly devastating; this results in ischemic medial injury, leading to aneurysmal dilation of the aorta and aortic annulus, and eventually valvular insufficiency.

✓ *better recognition and treatment of syphilis in its early stages have decreased the frequency of this complication*

Morphology

- *T. pallidum* has a prediliction to involve small blood vessels, the vasa vasorum, in the aortic adventitia. These vessels develop so-called **obliterative endarteritis.**

- The affected vessels show luminal narrowing and obliteration, scarring of the vessel wall, and a dense surrounding rim of lymphocytes and plasma cells that may extend into the media **(syphilitic aortitis)**. The spirochetes are difficult to demonstrate in tissues.

- The narrowing of the lumina of the vasa vasorum causes ischemic injury of the aortic media, with patchy loss of the medial elastic fibers and muscle cells, followed by inflammation and scarring.

- With destruction of the media, the aorta loses its elastic recoil and may become dilated, producing an aneurysm.

- Contraction of fibrous scars may lead to wrinkling of intervening segments of aortic intima, grossly reminiscent of "tree bark."

- Syphilitic involvement of the aorta favors the development of superimposed atherosclerosis of the aortic root, which can envelop and occlude the coronary ostia.

- With weakening of the aortic root, the valvular annulus becomes dilated, resulting in valvular insufficiency and massive volume overload hypertrophy of the left ventricle. The greatly enlarged hearts are sometimes called "cor bovinum" (cow's heart).

Thoracic aortic aneurysms (regardless of etiology) cause signs and symptoms referable to :

(1) encroachment on mediastinal structures,

(2) respiratory difficulties (dyspnea) caused by encroachment on the lungs and airways,

(3) difficulty in swallowing (dysphagia) caused by compression of the esophagus,

(4) persistent cough from irritation of the recurrent laryngeal nerves,

(5) pain caused by erosion of bone (i.e., ribs and vertebral bodies),

(6) cardiac disease due to valvular insufficiency or narrowing of the coronary ostia,

(7) aortic rupture. Most patients with syphilitic aneurysms die of heart failure induced by aortic valvular incompetence.

Aortic Dissection

- Aortic dissection is a catastrophic event whereby blood splays apart the laminar planes of the media to form a blood-filled channel within the aortic wall . this channel often ruptures through the adventitia and into various spaces, where it causes either massive hemorrhage or cardiac tamponade (hemorrhage into the pericardial sac).

- In contrast to atherosclerotic and syphilitic aneurysms, *aortic dissection may or may not be associated with aortic dilation*. Consequently, the older term "dissecting aneurysm" is discouraged.

- ***Aortic dissection occurs principally in two epidemiologic groups:***
    I. men aged 40 to 60 years, with antecedent hypertension (more than 90% of cases of dissection),
    II. younger patients with systemic or localized abnormalities of connective tissue affecting the aorta (e.g., Marfan syndrome-defect in fibrillin formation-).

Dissections can also:

- ✓ be iatrogenic (e.g., complicating arterial cannulations during diagnostic catheterization or cardiopulmonary bypass).

- ✓ Rarely, for unknown reasons, dissection of the aorta or other branches, including the coronary arteries, occurs during or after pregnancy.

- *Dissection is unusual in the presence of substantial atherosclerosis or other causes of medial scarring, such as syphilis, presumably because the medial fibrosis inhibits propagation of the dissecting hematoma.*

Pathogenesis

- Hypertension is the major risk factor for aortic dissection.

- A smaller number of dissections is related to inherited or acquired connective tissue disorders causing abnormal vascular ECM (e.g., Marfan syndrome, Ehlers-Danlos syndrome, vitamin C deficiency, copper metabolic defects).

    ✓ Among these, Marfan syndrome is probably the most common; it is an autosomal dominant disease of fibrillin, an ECM scaffolding protein required for normal elastic tissue synthesis. Patients have skeletal abnormalities (elongated axial bones) and ocular findings (lens subluxation) in addition to the cardiovascular manifestations.

- Aortas in hypertensive patients show medial hypertrophy of the vasa vasorum associated with ECM degenerative changes and variable loss of medial SMCs, suggesting that pressure-related mechanical injury and/or ischemic injury (due to diminished flow through the vasa vasorum) is somehow contributory.

    ✓ Occasionally, dissections occur in the setting of rather trivial medial degeneration, and conversely marked degenerative changes are frequently seen at autopsies of patients who are completely free from dissection.

- Regardless of the underlying etiology that causes medial weakness, the trigger for the intimal tear and initial intramural aortic hemorrhage is not known in most cases.

    • once the tear has occurred, blood flow under systemic pressure dissects through the media, fostering progression of the medial hematoma. Accordingly, aggressive pressure-reducing therapy may be effective in limiting an evolving dissection.

    • In some cases, disruption of penetrating vessels of the vasa vasorum can give rise to an intramural hematoma *without* an intimal tear.

Morphology

- the intimal tear marking the point of origin of the dissection is found in the ascending aorta, usually within 10 cm of the aortic valve.Such tears are usually transverse or oblique and 1 to 5 cm in length, with sharp, jagged edges.

- The dissection can extend along the aorta retrograde toward the heart as well as distally, sometimes all the way into the iliac and femoral arteries.

- The dissecting hematoma spreads characteristically along the laminar planes of the aorta, usually approximately between the middle and outer thirds. It often ruptures out through the adventitia, causing massive hemorrhage.

- In some instances, the dissecting hematoma reenters the lumen of the aorta, producing a second distal intimal tear and a new vascular channel within the media of the aortic wall (and resulting in a "double-barreled aorta" with a false channel). This averts a fatal extra-aortic hemorrhage. In the course of time, false channels may become endothelialized and can be recognized as chronic dissections.

- In most cases, no specific underlying causal pathology can be identified in the aortic wall. The most frequent pre-existing histologically detectable lesion is cystic medial degeneration (CMD).

  - ✓ CMD is characterized by elastic tissue fragmentation and separation of the elastic and SMC elements of the media by cystic spaces filled with the amorphous proteoglycan-rich ECM.

  - ✓ CMD of the aorta frequently accompanies Marfan syndrome

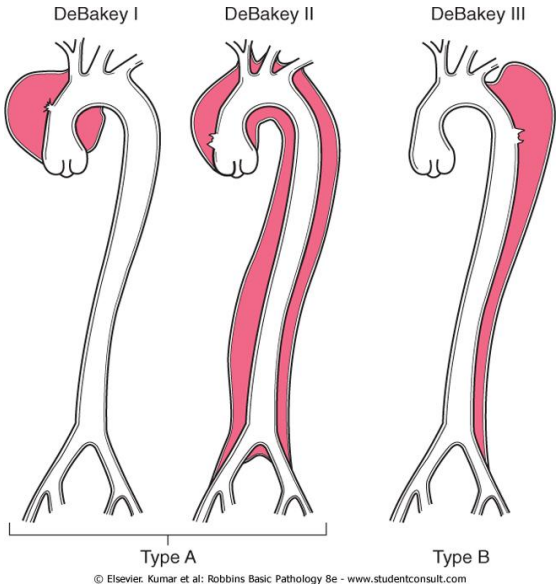
  - ✓ Inflammation is characteristically absent.

patients with dissection caused by hypertension have variable nonspecific changes in aortic wall histology ranging from mild fragmentation of elastic tissue (most commonly) to overt CMD

Clinical Course

- The risk and nature of serious complications of dissection depend strongly on the level of the aorta affected

- the most serious complications occur with dissections that involve the aorta from the aortic valve to the arch. Thus, aortic dissections are generally classified into **two types** :



I. proximal lesions (type A dissections):

- ✓ The more common (and dangerous).
- ✓ involving either the ascending aorta only or both the ascending and descending aorta.
- ✓ (types I and II of the DeBakey classification).

II. Distal lesions (type B dissections)::

- ✓ not involving the ascending part and usually beginning distal to the subclavian artery.
- ✓ (DeBakey type III).

- **Clinical symptoms** of aortic dissection are *sudden onset of excruciating pain,* usually beginning in the anterior chest, radiating to the back between the scapulae, and moving downward as the dissection progresses; the pain can be confused with that of myocardial infarction.

✓ The most common cause of death is rupture of the dissection outward into any of the three body cavities (i.e., pericardial, pleural, or peritoneal).

✓ Retrograde dissection into the aortic root can cause disruption of the aortic valvular apparatus. Thus, common clinical manifestations include :

- *cardiac tamponade, aortic insufficiency,* and *myocardial infarction* or *extension of the dissection into the great arteries* of the neck or into the coronary, renal, mesenteric, or iliac arteries, causing critical vascular obstruction; compression of spinal arteries may cause transverse myelitis.

ARTERIOSCLEROSIS

Arteriosclerosis (hardening of the arteries) is a generic term for thickening and loss of elasticity of arterial walls. It occurs in three forms:

1-(*ATH*) is the most frequent and important pattern .

2- much less clinical importance is(*Mönckeberg medial calcific sclerosis*), characterized by calcific deposits in muscular arteries in persons older than 50 years. These radiographically visible, often palpable calcifications do not encroach on the vessel lumen.

3-Disease of small arteries and arterioles *(arteriolosclerosis)* is the third pattern. Two anatomic variants, hyaline and hyperplastic arteriolosclerosis, cause thickening of vessel walls with luminal narrowing that may induce downstream ischemic injury. Most often associated with hypertension and diabetes.

- Atherosclerosis is characterized by intimal lesions called *atheromas*, or *atheromatous* or *fibrofatty plaques*, that protrude into and obstruct vascular lumina, weaken the underlying media, and may undergo serious complications. Global in distribution, ATH overwhelmingly contributes to more mortality-approximately half of all deaths-and serious morbidity in the Western world than any other disorder. Because coronary artery disease is an important manifestation of ATH, *epidemiologic data on ATH are expressed largely in terms of the incidence of the number of deaths caused by ischemic heart disease (IHD)* . Indeed, myocardial infarction alone is responsible for 20% to 25% of all deaths in the United States.

Clinical Significance

ATH primarily affects elastic arteries (e.g., aorta, carotid, and iliac arteries) and large and medium-sized muscular arteries (e.g., coronary and popliteal arteries). *Symptomatic atherosclerotic disease most often involves the arteries supplying the heart, brain, kidneys, and lower extremities. Myocardial infarction (heart attack), cerebral infarction (stroke), aortic aneurysms, and peripheral vascular disease (gangrene of the legs) are the major consequences of ATH.* ATH also takes a toll through other consequences of acutely or chronically diminished arterial perfusion, *such as mesenteric occlusion, sudden cardiac death, chronic IHD, and ischemic encephalopathy.*

I n small arteries, atheromas can occlude lumina, compromise blood flow to distal organs, and cause ischemic injury. Moreover, atherosclerotic plaques can undergo disruption and precipitate thrombi that further obstruct blood flow.

In large arteries, plaques are destructive, encroaching on the subjacent media and weakening the affected vessel wall, causing aneurysms that may rupture. Moreover, extensive atheromas are friable, often yielding emboli into the distal circulation.

Considerable progress on the health impact of ATH-related disease has been made over the past decades in the United States and elsewhere. Between 1963 and 2000 there has been an approximately 50% decrease in the death rate from IHD and a 70% decrease in death from strokes, a reduction in mortality that increased the average life expectancy in the United States by 5 years. Three factors have contributed to this impressive improvement: (1) prevention of ATH through changes in life style, including reduced cigarette smoking, altered dietary habits with reduced consumption of cholesterol and saturated animal fats, and control of hypertension; (2) improved methods of treatment of myocardial infarction and other complications of IHD; and (3) prevention of recurrences in patients who have previously suffered serious ATH-related clinical events.

Epidemiology and Risk Factors.

Virtually ubiquitous among most developed nations, ATH is much less prevalent in Central and South America, Africa, and Asia. The mortality rate for IHD in the United States is among the highest in the world and is six times higher than that in Japan. Interestingly, Japanese who emigrate to the United States and adopt the life styles and dietary customs of their new home acquire the predisposition to ATH typical of the American population.

The prevalence and severity of the disease among individuals and groups are related to a number of factors, some constitutional and therefore immutable but others acquired and potentially capable of control . The constitutional factors include age, sex, and genetics.

Age is a dominant influence. Death rates from IHD rise with each decade even into advanced age. ATH is not usually clinically evident until middle age or later, when the arterial lesions precipitate organ injury. Between ages 40 and 60 the incidence of myocardial infarction increases five-fold.

Other factors being equal, men are much more prone to ATH and its consequences than are women. Myocardial infarction and other complications of ATH are uncommon in premenopausal women unless they are predisposed by diabetes, hyperlipidemia, or severe hypertension. After menopause, however, the incidence of ATH-related diseases increases, probably owing to a decrease in natural estrogen levels. Indeed, the frequency of myocardial infarction in the two sexes equalizes by the seventh to eighth decade of life. Some protection against ATH is afforded by postmenopausal hormone replacement therapy .

The well-established familial predisposition to ATH and IHD is most likely polygenic. In some instances it relates to familial clustering of other risk factors, such as hypertension or diabetes, whereas in others it involves well-defined hereditary genetic derangements in lipoprotein metabolism that result in excessively high blood lipid levels, such as familial hypercholesterolemia .

Although the aforementioned factors are unchangeable in an individual, *other risk factors, particularly diet, life style, and personal habits, are to a large extent amenable to control.* The four major risk factors that can be modified are*(hyperlipidemia, hypertension, cigarette smoking, and diabetes.)*

Hyperlipidemia

is a major risk factor for ATH. Most of the evidence specifically implicates *hypercholesterolemia.* The major component of the total serum cholesterol associated with increased risk is low-density lipoprotein (LDL) cholesterol. In contrast, the higher the level of high-density lipoprotein (HDL), the lower is the risk. HDL is believed to mobilize cholesterol from developing an existing atheroma and transport it to the liver for excretion in the bile, thereby earning its designation as the "good cholesterol." There is thus great interest in dietary, pharmacologic, and behavioral methods of lowering serum LDL and raising serum HDL. Both exercise and moderate consumption of ethanol raise the HDL level, whereas obesity and smoking lower it.

Major Risks	Lesser, Uncertain, or Nonquantitated Risks
Nonmodifiable	Obesity
Increasing age	Physical inactivity
Male gender	Stress ("type A" personality)
Family history	Postmenopausal estrogen deficiency
Genetic abnormalities	High carbohydrate intake
Potentially Controllable	Lipoprotein(a)
Hyperlipidemia	Hardened (trans) unsaturated fat intake
Hypertension	Chlamydia pneumoniae

Hypertension

is a major risk factor for ATH at all ages. Men ages 45 to 62 whose blood pressure exceeds 169/95 mm Hg have a more than five-fold greater risk of IHD than those with blood pressures of 140/90 mm Hg or lower. Both systolic and diastolic levels are important in increasing risk. Antihypertensive therapy reduces the incidence of ATH-related diseases, particularly strokes and IHD.

Cigarette smoking

is a well-established risk factor in men and is thought to account for the relatively recent increase in the incidence and severity of ATH in women. When one or more packs of cigarettes are smoked per day for several years, the death rate from IHD increases by up to 200%. Cessation of smoking reduces the increased risk substantially.

Diabetes mellitus

induces hypercholesterolemia and a markedly increased predisposition to ATH. Other factors being equal, the incidence of myocardial infarction is twice as high in diabetics as in nondiabetics. There is also an increased risk of strokes and, even more striking, perhaps a 100-fold increased risk of ATH-induced gangrene of the lower extremities.

- Patients with *homocystinuria*, rare inborn errors of metabolism resulting in high levels of circulating homocysteine (>100 μmol/L), have premature vascular disease .

(There is a relationship between total serum homocysteine levels and coronary artery disease)

- Hyperhomocystinemia can be caused by low folate and vitamin B intake, and some evidence (obtained in women) suggests that ingestion of folate and vitamins B_6 and B_{12} beyond conventional dietary recommendations may reduce the incidence of cardiovascular disease. However, firm data on the benefit of dietary supplementations to reduce homocysteine levels are lacking.

Additional Factors Affecting Hemostasis/Thrombosis.

Epidemiologic evidence also indicates that several markers of hemostatic and thrombotic function are potent predictors of risk for major atherosclerotic events, including myocardial infarction and stroke. Such markers include those related to fibrinolysis (e.g., elevated plasminogen activator inhibitor 1) and inflammation (e.g., C-reactive protein).

Lipoprotein a [Lp(a)] is an altered form of LDL that contains the apolipoprotein B-100 portion of the LDL linked to apolipoprotein A (apo A). Epidemiologic studies suggest a correlation between increased blood levels of lipoprotein Lp(a) and coronary and cerebrovascular disease, independent of the level of total cholesterol or LDL.

Other Factors.

Factors associated with a less pronounced and/or difficult-to-quantitate risk include lack of exercise; competitive, stressful life style with ***"type A" personality behavior***; and unrestrained weight gain (largely because obesity induces hypertension, diabetes, hypertriglyceridemia, and decreased HDL). Epidemiologic data also indicate a protective role for moderate intake of alcohol.

Multiple risk factors have a multiplicative effect; two risk factors increase the risk approximately fourfold. When three risk factors are present (e.g., hyperlipidemia, hypertension, and smoking), the rate of myocardial infarction is increased seven times. However, ATH and its consequences may develop in the absence of any apparent risk factors, so that even those who live "the prudent life" and have no apparent genetic predispositions are not immune to this killer disease.

Pathogenesis.

Understandably, the overwhelming clinical importance of ATH has stimulated enormous efforts to discover its cause. Historically, two hypotheses for atherogenesis were dominant: one emphasized cellular proliferation in the intima, whereas the other emphasized organization and repetitive growth of thrombi. The contemporary view of the pathogenesis of ATH incorporates elements of both older theories and accommodates the risk factors previously discussed. This concept, called *the response to injury hypothesis, considers ATH to be a chronic inflammatory response of the arterial wall initiated by injury to the endothelium* . Central to this thesis are the following:

- *Chronic endothelial injury*, usually subtle, with resultant endothelial dysfunction, yielding increased permeability, leukocyte adhesion, and thrombotic potential.
- Insudation of *lipoproteins* into the vessel wall, mainly LDL with its high cholesterol content.
- Modification of lesional lipoproteins by *oxidation* (see later).
- Adhesion of *blood monocytes* (and other leukocytes) to the endothelium, followed by their migration into the intima and their transformation into *macrophages* and *foam cells.*
- Adhesion of *platelets.*
- Release of factors from activated platelets, macrophages, or vascular cells that cause *migration of SMCs* from media into the intima.
- *Proliferation of SMCs* in the intima, and elaboration of extracellular matrix, leading to *accumulation of collagen and proteoglycans.*
- *Enhanced accumulation of lipids* both within cells (macrophages and SMCs) and extracellularly.

The Role of Endothelial Injury.

Chronic or repetitive endothelial injury is the cornerstone of the response to injury hypothesis. Endothelial injury induced in experimental animals by mechanical denudation, hemodynamic forces, immune complex deposition, irradiation, and chemicals causes intimal thickening and, in the presence of high-lipid diets, typical atheromas. However, *early human lesions begin at sites of morphologically intact endothelium.* Thus, nondenuding endothelial dysfunction causing increased endothelial permeability, enhanced leukocyte adhesion, and alterations in expression of EC gene products is critical to the human disease.

The specific cause of endothelial dysfunction in early ATH is unknown: potential culprits include circulating derivatives of cigarette smoke, homocysteine, and possibly viruses and other infectious agents. However, the two most important determinants of endothelial alterations, perhaps acting in concert, are thought to be hemodynamic disturbances that accompany normal circulatory function and adverse effects of hypercholesterolemia.

The Role of Lipids.

It should be recalled that the various classes of blood lipids are transported as lipoproteins complexed to specific apoproteins. Dyslipoproteinemias result either from mutations that yield defective apolipoproteins or from some other underlying disorder, such as the nephrotic syndrome, alcoholism, hypothyroidism, or diabetes mellitus. Examples of lipoprotein abnormalities frequently found in the population (and, indeed, present in many myocardial infarction survivors) are:

(1) increased LDL cholesterol levels, (2) decreased HDL cholesterol levels, and (3) increased levels of the abnormal Lp(a) .

The major evidence implicating hypercholesterolemia in the genesis of (AS) includes the following:

- **Genetic defects in lipoprotein metabolism** causing hyperlipoproteinemia are associated with accelerated ATH. For example, homozygous familial hypercholesterolemia .
- **Other genetic or acquired disorders** (e.g., diabetes mellitus, hypothyroidism) that cause hypercholesterolemia lead to premature and severe ATH.
- The major lipids in atheromas (plaques) are plasma-derived cholesterol and cholesterol esters.
- **Epidemiologic analyses** demonstrate a significant correlation between the severity of ATH and the levels of total plasma cholesterol or LDL cholesterol.
- **Lowering levels of serum cholesterol** by diet or drugs slows the rate of progression of ATH, causes regression of some plaques, and reduces the risk of cardiovascular events. Indeed, lowering cholesterol increases overall survival and reduces risk of ATH-related events in patients with established coronary heart disease with elevated or average cholesterol levels, as well as in patients with hypercholesterolemia but without overt ATH-related disease.

The mechanisms by which hyperlipidemia contributes to atherogenesis include the following:

- Chronic hyperlipidemia, particularly hypercholesterolemia, may directly impair EC function through increased production of oxygen free radicals that deactivate nitric oxide, the major endothelial-relaxing factor.
- With chronic hyperlipidemia, lipoproteins accumulate within the intima at sites of increased endothelial permeability.
- Chemical changes of lipid induced by free radicals generated in macrophages or EC in the arterial wall yield *oxidized (modified) LDL*. Oxidized LDL (1) is ingested by macrophages through the *scavenger receptor,* distinct from the LDL receptor thus forming foam cells; (2) increases monocyte accumulation in lesions; (3) stimulates release of growth factors and cytokines; (4) is cytotoxic to ECs and SMCs; and (5) can induce endothelial cell dysfunction.

Consistent with the role of oxidant stress is the finding that coronary arterial ATH may be decreased by antioxidant vitamins (β-carotene and vitamin E). It should be noted, however, that data are insufficient to recommend dietary supplementation with antioxidants for the prevention of ATH.

The Role of Macrophages.

Monocytes and macrophages play a key role in ATH. These cells are:

- *Adhere* to endothelium early in ATH by means of specific endothelial adhesion molecules induced on the surface of dysfunctional ECs.
- *Migrate* between ECs to localize in the intima.

- *Transform* into macrophages and avidly engulf lipoproteins, largely oxidized LDL, to become foam cells.

Macrophages also produce interleukin 1 and tumor necrosis factor, which increase adhesion of leukocytes; several chemokines generated by macrophages (e.g., monocyte chemoattractant protein 1) may further recruit leukocytes into the plaque. Macrophages produce toxic oxygen species that also cause oxidation of the LDL in the lesions, and they elaborate growth factors that may contribute to SMC proliferation. T lymphocytes (both CD4+ and CD8+) are also present in atheromas, but their role is uncertain.

The Role of Smooth Muscle Cell Proliferation.

SMC proliferation and the extracellular matrix that SMCs deposit in the intima convert a fatty streak into a mature fibrofatty atheroma and contribute to the progressive growth of atherosclerotic lesions. Several growth factors have been implicated in the proliferation of SMCs, including platelet-derived growth factor (released by platelets adherent to a focus of endothelial injury, and macrophages, ECs, and SMCs), fibroblast growth factor, and transforming growth factor α.

The development of the atheromatous plaque could also be explained if SMC proliferation were in fact the primary event. oligoclonal. One interpretation of oligoclonality is that plaques may be equivalent to benign neoplastic growths, perhaps induced by an exogenous chemical (e.g., cholesterol or some of its oxidized products) or an oncogenic virus.

Infection.

Infectious processes could contribute to ATH, but this thesis has not been proved. Microbiologic organisms, including herpesvirus, cytomegalovirus, and *Chlamydia pneumoniae*, have been detected in atherosclerotic plaque but not in normal arteries. It has been suggested that the infectious organism incites a chronic inflammatory process

that contributes to atheroma formation. Evidence for participation of *C. pneumoniae* is strongest;(studies suggest that antibiotic therapy appropriate for this organism reduces recurrent clinical events in patients with IHD).

The previous discussion emphasizes that the evolving atheroma is a dynamic and complex lesion containing chronic inflammatory cells (macrophages, lymphocytes), ECs, and SMCs, all expressing or contributing a variety of factors that could play roles in the pathogenesis of these lesions. At an early stage, the intimal plaque is an aggregation of foam cells of macrophage and SMC origin, some of which have died and released lipid and debris, surrounded by SMCs. With progression, the atheroma is modified by SMC-synthesized collagen and proteoglycans. Connective tissue is particularly prominent on the intimal aspect, producing the fibrous cap, but many lesions retain a central core of lipid-laden cells and fatty debris. Disruption of the fibrous cap with superimposed thrombus is often associated with catastrophic clinical events.

The major proposed cellular mechanisms of atherogenesis. This schema considers ATH a chronic inflammatory response of the vascular wall to a variety of events that are initiated early in life. Multiple mechanisms contribute to plaque formation and progression, including endothelial dysfunction, monocyte adhesion and infiltration, lipid accumulation and oxidation, SMC proliferation, extracellular matrix deposition, and thrombosis.

Prevention:

Efforts to reduce the consequences and impact of ATH include *primary prevention* programs aimed at either delaying atheroma formation or causing regression of established lesions in persons who have never suffered a serious complication of atherosclerotic coronary heart disease, and *secondary prevention* programs intended to prevent recurrence of events such as myocardial infarction in patients with symptomatic disease.

As detailed earlier, there is ample justification for the following recommendations for primary prevention of ATH-related complications in adults by virtue of risk factor modification: abstention from or cessation of cigarette smoking; control of hypertension; weight reduction and increased exercise; and, most importantly, lowering total and LDL blood cholesterol levels while increasing HDL.

Moreover, several lines of evidence suggest that risk factor examination and prevention directed at modification of risk should begin in **childhood**:

- Morphologic studies have established that atherosclerotic coronary artery disease begins in childhood.
- Cardiovascular risk factors in children predict the adult profile and have distinct ethnic and sex differences that relate to adult heart disease.
- Serum cholesterol concentrations and smoking are important determinants of the early stages of ATH noted at autopsy in adolescents and young adults.

Secondary prevention involves use of lipid-lowering drugs (statins) and use of antiplatelet drugs. These can successfully reduce recurrent myocardial infarctions.

Clinicopathologic Effects of Atherosclerotic Coronary Artery Disease.

The down-stream complications of atherosclerotic coronary artery disease occur through impaired coronary perfusion relative to myocardial demand (*myocardial ischemia*). *The vascular changes comprise a complex dynamic interaction among fixed atherosclerotic narrowing of the epicardial coronary arteries, intraluminal thrombosis overlying a disrupted atherosclerotic plaque, platelet aggregation, and vasospasm*.

***MORPHOLOGY*:**

the major components of well-developed atheromatous plaque:

1- fibrous cap composed of proliferating smooth muscle cells, macrophages, lymphocytes, foam cells, and extracellular matrix.

2-The necrotic core consists of cellular debris, extracellular lipid with cholesterol crystals, and foamy macrophages.

Histologic features of atheromatous plaque in the coronary artery:

1- Overall architecture demonstrating fibrous cap and

2-a central lipid core with

3- typical cholesterol clefts. The lumen has been moderately narrowed.

The key processes in ATH are intimal thickening and lipid accumulation giving rise to atheroma. These are described first; discussed subsequently is fatty streak, the presumed precursor lesion for atheromas. An **atheroma** or atheromatous plaque consists of a raised focal lesion initiating within the intima, having a soft, yellow, grumous core of lipid (mainly cholesterol and cholesterol esters) and covered by a firm, white fibrous cap. Also called fibrous, fibrofatty, lipid, or fibrolipid plaques, atheromatous plaques appear white to whitish yellow and impinge on the lumen of the artery. They vary in size from 0.3 to 1.5 cm in diameter but sometimes coalesce to form larger masses. Atherosclerotic lesions usually involve the arterial wall only partially around its circumference ("eccentric" lesions) and are patchy and variable along the vessel length. Focal and sparsely distributed at first, atherosclerotic lesions become more and more numerous and diffuse as the disease advances.

In the characteristic distribution of atherosclerotic plaques in humans, *the abdominal aorta is usually much more involved than is the thoracic aorta*, and lesions tend to be much more prominent around the origins (ostia) of major branches. In descending order (after the lower abdominal aorta), the most extensively involved vessels are the coronary arteries, the popliteal arteries, the internal carotid arteries, and the vessels of the circle of Willis. Vessels of the upper extremities are usually spared, as are the mesenteric and renal arteries, except at their ostia. Nevertheless, in an individual case, the severity of AS in one artery does not predict its severity in another.

Atherosclerotic plaques have three principal components: (1) cells, including SMCs, macrophages, and other leukocytes; (2) extracellular matrix, including collagen, elastic fibers, and proteoglycans; and (3) intracellular and extracellular lipid

. **Foam cells** are large lipid-laden cells that derive predominantly from blood monocytes (tissue macrophages), but SMCs can also imbibe lipid to become foam cells. Finally, particularly around the periphery of the lesions, there is usually evidence of **neovascularization** (proliferating small blood vessels). Typical atheromas contain relatively abundant lipid, but many so-called fibrous plaques are composed mostly of SMCs and fibrous tissue

Plaques generally continue to change and progressively enlarge through cell death and degeneration, synthesis and degradation (remodeling) of extracellular matrix, and organization of thrombus. Moreover, atheromas often undergo calcification. Patients with advanced coronary calcification (as determined by computed tomography) appear to be at increased risk for coronary events

The advanced lesion of ATH is the most vulnerable to the following pathologic changes that have clinical significance:

- Focal **rupture, ulceration, or erosion** of the luminal surface of atheromatous plaques may result in exposure of highly thrombogenic substances that induce thrombus formation or discharge of debris into the bloodstream, producing microemboli composed of lesion contents **(cholesterol emboli or atheroemboli).**
- **Hemorrhage** into a plaque may occur, especially in the coronary arteries.
- Superimposed **thrombosis,** the most feared complication, usually occurs on disrupted lesions (those with rupture, ulceration, erosion, or hemorrhage) and may partially or completely occlude the lumen .
- **Aneurysmal dilation** may result from ATH-induced pressure or ischemic atrophy of the underlying media .
- **Fatty streaks,** composed of lipid-filled foam cells, are not significantly raised and thus do not cause any disturbance in blood flow.

Best wish's

Dr.Burke