Diseases of Cardiovascular System (CVS)
➤ Diseases of Blood Vessels

➤ Diseases of Heart
Diseases of Blood Vessels
Vascular disease is responsible for more morbidity and mortality than any other category of human disease.

Most clinically significant lesions involve arteries; venous pathology can also cause disorders.
Two Principal Mechanisms Involved in Vascular Disease

I. Narrowing or Complete Obstruction of Vessel Lumina
   This obstruction occurs in two ways
   a. Progressively: e.g., by Atherosclerosis
      OR
   b. Precipitously: e.g., by Thrombosis or Embolism

II. Weakening of Vessel Walls, causing dilation and/or rupture
Diseases of Blood Vessels - Overview

1. Normal Vessels
2. Congenital Anomalies
3. Vascular Wall Cells and Their Response to Injury
4. Arteriosclerosis
5. Atherosclerosis
6. Hypertensive Vascular Disease
7. Aneurysms and Dissection
8. Vasculitis
9. Raynaud Phenomenon
10. Veins and Lymphatics
11. Tumours
12. Pathology of Vascular Intervention
Diseases of Blood Vessels
NORMAL VESSELS

- The general architecture and cellular composition of blood vessels are the same throughout the cardiovascular system

HOWEVER

- Distinct functional requirements in different locations within the vasculature result in multiple forms of vascular specializations
NORMAL VESSELS

- As arteries narrow to arterioles, the ratio of wall thickness to lumen increases, to allow more precise regulation of intravascular pressures.

- Veins on the other hand are distensible thin-walled vessels with high capacitance.
AS AN EXAMPLE:
Arterial walls are thicker than corresponding veins at the same level of branching to accommodate pulsatile flow and higher blood pressures.

AS A RESULT
Due to these vessels’ specialization the pathologic lesions within the vascular tree characteristically affect only certain parts of the circulation.
THUS

- Atherosclerosis affects mainly elastic and muscular arteries

- Hypertension affects small muscular arteries and arterioles

- Specific types of vasculitis characteristically involve only vessels of a certain caliber
Endothelial cells and smooth muscle cells constitute the bulk of vessels wall cellularity.

Reminder of the wall is composed of extracellular matrix including elastin, collagen and glycosaminoglycans.
Vessel walls are organized into three concentric layers:

(i) Intima; (ii) Media; (iii) Adventitia

**INTIMA:** Consists of and endothelial cells monolayer overlying a thin extracellular matrix sheet. The intima is demarcated from the media by a dense elastic membrane called internal elastic lamina.

**MEDIA:** It is composed predominantly of smooth muscle cells and extracellular matrix, surrounded by relatively loose connective tissue, nerve fibers, and small vessels of adventitia.

**ADVENTITIA:** Composed of nerve fiber, nutrient vessels (vasa-vasorum).
The vascular wall

A: Cross-section from a muscular artery

B: Histology showing an artery (A) and adjacent vein (V), with the elastic lamellae stained black. Because it must sustain higher pressures, the artery has a thicker wall with more organized elastin architecture than in the corresponding vein. Conversely, the vein has a larger lumen with diffusely distributed elastin, permitting greater capacitance.
VESSEL WALL

- Tunica adventitia
  - Connective tissue
- Tunica intima
  - Endothelium
  - Internal elastic lamina
- External elastic lamina
  - Smooth muscle cells
  - Tunica media
TYPES OF ARTERIES

Large OR Elastic Arteries
- Examples:
  - Aorta and its major branches
  - Pulmonary Artery
- Structure:
  Elastic fibers alternate in layers with smooth muscle cells

Medium Sized OR Muscular Arteries
- Examples:
  - Renal Artery
  - Corneal Artery
  - Brachial Artery
- Structure:
  Media is composed primarily of smooth muscle cells, with elastin limited to the internal and external elastic lamina

Small Arteries & Arterioles
- Examples:
  - Lie within the intestinal connective tissue of organs
- Structure:
  Media here is essentially all smooth muscle cells
Although all vessels share the same general constituents, the thickness and composition of the various layers differ as a function of haemodynamic forces and tissue requirements.
Arterioles are the principal control points for regulation of physiologic resistance to blood flow.

In arterioles, the pressure and velocity of blood flow are both sharply reduced, and the flow becomes steady rather than pulsatile.
CAPILLARIES

- Represent the level of vascular branching after arterioles

- These are approximately the diameter of red blood cell (7-8 um) They have an endothelial lining but no media
LYMPHATICS

- Thin walled, endothelium lined channels

- Drain excess interstitial tissue fluid eventually returning it to blood via the thoracic duct
Diseases of Blood Vessels

VASCULAR WALL CELLS & THEIR RESPONSE TO INJURY
Endothelial cells and smooth muscle cells play central roles in vascular biology and pathology.

The integrated function of these cells is critical for vasculature to adapt to haemodynamic and biochemical stimuli.
Endothelial Cells

Vascular endothelium is a versatile multifunctional tissue having many synthetic and metabolic properties:

1. Serve as a semipermeable membrane, controlling the transfer of small and large molecules
2. Maintain non-thrombogenic blood vessels interface by regulating thrombosis, thrombolysis and platelet adherence.
3. Modulate vascular tone and blood flow.
4. Metabolize hormones
5. Regulate immune and inflammatory reactions
6. Modify lipoproteins in the artery wall.
7. Regulate the growth of other cells types, particularly smooth muscle cells

**ENDOTHELIAL INJURY IS CRITICAL TO THE INITIATION OF ATHEROSCLEROSIS AND THE VASCULAR EFFECTS OF HYPERTENSION AND OTHER DISORDERS**
## Endothelial Cells – Properties and Functions

<table>
<thead>
<tr>
<th>Property/Function</th>
<th>Mediator/Products</th>
</tr>
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<tbody>
<tr>
<td>Maintenance of permeability barrier</td>
<td></td>
</tr>
<tr>
<td>Elaboration of anticoagulant, antithrombogenic, fibrinolytic regulators</td>
<td>Prostacyclin; Thrombomodulin; Heparin-like molecule; Plasminogen activator</td>
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<tr>
<td>Elaboration of prothrombotic molecules</td>
<td>Von Willebrand Factor; Tissue factor</td>
</tr>
<tr>
<td>Extracellular matrix production</td>
<td>Collagen; Proteoblucans</td>
</tr>
<tr>
<td>Modulation of blood flow and vascular reactivity</td>
<td>Vasoconstrictors; endothelin; ACE; Vasodilators; NO; Prostacyclin</td>
</tr>
<tr>
<td>Regulation of inflammation and immunity</td>
<td>IL-1; IL-6; Chemokines; Adhesion molecules; VCAM-1; ICAM; E-selection; P-Selection</td>
</tr>
<tr>
<td>Regulation of cell growth</td>
<td>Growth Stimulators: PDGF; CSF; FGF</td>
</tr>
<tr>
<td></td>
<td>Growth Inhibitors: Heparin; TGF-β</td>
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</table>

ACE: Angiotensin Converting Enzyme; CSF: Colony Stimulating Factor; FGF: Fibroblast Growth Factor; ICAM: Intercellular Adhesion Molecule; IL: Interleukin; LDL: Low Density Lipoprotein; NO: Nitric Oxide; PDGF: platelet Derived Growth Factor; TGF: Transforming Growth factor β; VCAM: Vascular Cell Adhesion Molecule
Different stimuli activates endothelial cells and induce vascular injury.

In turn activated endothelial cells release different molecules and gene products with varied biologic activities.
Normal blood pressure, laminar flow and stable growth factor levels promote a basal endothelial cell state that maintains a non-thrombotic surface and appropriate vascular wall smooth muscle tone. Injury or exposure to certain mediators result in endothelial activation, a state in which endothelial have adhesive, pro-cogulant surfaces and release factors that lead to smooth muscle contraction and/or proliferation and matrix synthesis.
VASCULAR SMOOTH MUSCLE CELLS

Vascular smooth muscle cells are capable of many functions, including:

1) Vasoconstriction and dilation in response to normal or pharmacologic stimuli
2. Synthesis of collagen and cytokines
3. Migration to the intima and proliferation

As the predominant cellular element of the vascular media, smooth muscle cells constitute an important element of not only normal vascular repair, but also pathologic processes such as atherosclerosis.
INTIMAL THICKENING: A STEROTYPED RESPONSE TO VASCULAR INJURY

- Following endothelial injury smooth muscle cells or smooth muscle cell precursor cells migrate into intima, proliferate and synthesize extracellular matrix in much the same way that fibroblasts fill in a wound forming a **neointima**.
- This sterotyped healing response results in intimal thickening that may be permanent.
- With persistent or recurrent insults, excessive thickening can cause stenosis of small and medium-sized blood vessels (e.g., atherosclerosis) that impedes downstream tissue perfusion.
## Summary: Vascular Structure and Function

<table>
<thead>
<tr>
<th>Vascular Structure and Function</th>
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<tbody>
<tr>
<td>All vessels are lined by endothelium; although all endothelial cells share certain homeostatic properties, endothelial cells in specific vascular beds have special features that allow for tissue-specific functions (e.g., fenestrated endothelial cells in renal glomeruli)</td>
</tr>
<tr>
<td>The relative smooth muscle cell and matrix content of vessel walls (e.g., in arteries, veins and capillaries) vary according to hemodynamic demands (e.g., pressure, pulsatility and functional requirements)</td>
</tr>
<tr>
<td>Endothelial cell function is tightly regulated in both the basal and activated states. Various physiologic and patho-physiologic stimuli induce endothelial activation and dysfunction that alter the endothelial cell phenotype (e.g., pro-versus anticoagulative Pro-versus anti-inflammatory, non-adhesive versus adhesive)</td>
</tr>
</tbody>
</table>
Diseases of Blood Vessels

CONGENITAL ANOMALIES
CONGENITAL ANOMALIES
OF BLOOD VESSELS

- Variants of usual anatomic pattern of vascular supply
- Rarely Symptomatic
- Can become important during surgery when a vessels in an unexpected location is injured.

- Three are particularly important
  1. Developmental OR Berry Aneurysms
  2. Arteriovenous Fistulas
  3. Fibromuscular Dysplasia
1. Developmental or Berry Aneurysms

- Small, spherical dilatations
- Occurs in cerebral vessels.
- Typically in circle of Willis
- When ruptured, they can cause fatal intracerebral haemorrhage
2. **Arteriovenous Fistulas**

- Abnormal, typically small direct connections between arteries and veins
- Bypass the intervening capillaries

- When arteriovenous fistulas are large or extensive, they can become clinically significant by shunting blood from the arterial to the venous circulation

- This forces the heart to pump additional volume, and high output cardiac failure can ensue
3. **Fibromuscular Dysplasia**

- Focal irregular thickening of the walls of medium and large muscular arteries, including renal, carotid, splanchnic and vertebral vessels

- Segments of the vessel wall are focally thickened by the combination of irregular medial and intimal hyperplasia and fibrosis

- Results in luminal stenosis
Diseases of Blood Vessels

ARTERIOSCLEROSIS
Arteriosclerosis literally means “hardening of the arteries”

It is a generic term reflecting arterial wall thickening and loss of elasticity.

Three patterns are recognized, with different clinical and pathologic consequences:
1. Arteriolosclerosis
2. Monckeberg Medial Calcific Sclerosis
3. Atherosclerosis
ARTERIOSCLEROSIS- Three Types

1. Arteriolosclerosis:
   - It effects small arteries and arterioles.

   - The two anatomic variants:
     (i) Hyaline
     (ii) Hyperplastic.

   - Both types are associated with vessel wall thickening and luminal narrowing that may cause downstream ischemic injury.

   - Two conditions commonly associated with arteriolosclerosis:
     (i) Hypertension
     (ii) Diabetes Mellitus
2. **Monckeberg Medial Calcific Scleriosis**

- Characterized by calcific deposits in muscular arteries
- The radiographically visible, often palpable calcifications, do not encroach on the vessel lumen and are usually not clinically significant

Monckeberg's medial calcific scleriosis is seen in this artery to the right of thyroid tissue at the left. This finding occurs most often in the elderly and is of no clinical significance, other than that the calcified arteries may be visualized on radiographs, and you need to know what is represented. Calcium deposits collect in the media of muscular arteries, particularly in pelvis and neck.
Atherosclerosis

- From Greek words for “gruel” and “hardening”
- Most frequent and clinically important pattern
Diseases of Blood Vessels

ATHEROSCLEROSIS
ATHEROCLEROSIS

- Atherosclerosis or Atheroma is the term used to describe a disease of large and medium-sized arteries, characterized by fibrosis, lipid deposition and chronic inflammation.

- An atheromatous plaque consists of a raised lesion with a soft, yellow, grumous core of lipid (mainly cholesterol and cholesterol esters) covered by a firm, white fibrous cap.

The major components of a well-developed intimal atheromatous plaque: fibrous cap composed of proliferating smooth muscle cells. Macrophages, lymphocytes, foam cells, and extracellular matrix. The necrotic core consists of cellular debris, extracellular lipid with cholesterol crystals and foamy macrophages.
Besides obstructing blood flow, atherosclerotic plaques weaken the underlying media and can themselves rupture, causing acute catastrophic vessel thromboses.

Atherosclerosis overwhelmingly causes more morbidity and mortality (roughly half the deaths) in the Western world than any other disorder.

Atheroma of the coronary arteries, "Coronary Heart Disease" is one of the commonest causes of deaths in many societies.

As atheroma causes narrowing or obstruction of many different arteries, a wide range of clinical disorders result.

Because coronary artery disease is an important manifestation of the, epidemiologic data related to atherosclerosis mortality typically reflect deaths by Ischemic Heart Disease.
Complications of Atherosclerosis

- Cerebral infarction
- Carotid atheroma—emboli causing transient ischaemic attacks or cerebral infarcts
- Myocardial infarction, cardiac failure
- Aortic aneurysms—rupture causes sudden death
- Peripheral vascular disease with intermittent claudication
- Gangrene
# Atherosclerosis OR Ischemic Heart Disease – Risk Factors

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
<th>Lesser, Uncertain, or Nonquantitiated Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonmodifiable</strong></td>
<td></td>
</tr>
<tr>
<td>➢ Increasing Age</td>
<td>➢ Obesity</td>
</tr>
<tr>
<td>➢ Male Gender</td>
<td>➢ Physical Inactivity</td>
</tr>
<tr>
<td>➢ Family History</td>
<td>➢ Stress (Type A personality)</td>
</tr>
<tr>
<td>➢ Genetic Abnormalities</td>
<td>➢ Postmenopausal Estrogen Deficiency</td>
</tr>
<tr>
<td><strong>Potentially Controllable</strong></td>
<td></td>
</tr>
<tr>
<td>➢ Hyperlipidemia</td>
<td>➢ High Carbohydrate Intake</td>
</tr>
<tr>
<td>➢ Hypertension</td>
<td>➢ Lipoprotein(a)</td>
</tr>
<tr>
<td>➢ Cigarette Smoking</td>
<td>➢ Hardened (trans) unsaturated fat intake</td>
</tr>
<tr>
<td>➢ Diabetes</td>
<td>➢ Chlamydia Pneumoniae</td>
</tr>
<tr>
<td>➢ Inflammation</td>
<td>➢ Infection</td>
</tr>
</tbody>
</table>
Age

- Although atherosclerosis is not usually clinically evident until middle age or alter, when the lesions precipitate organ injury, it is slowly progressive disease that begins in childhood and develops slowly over decades.
Gender

- Premenopausal women are relatively protected against atherosclerosis and its consequences compared with middle aged men, unless predisposed due to hypertension, diabetes mellitus, hyperlipidemia, etc.

- After menopause the incidence increases in women with increasing age. With greater age eventually exceeds that of men.
In some instances it relates to familial clustering of other risk factors, such as hypertension or diabetes, whereas in others it involves well-defined genetic derangements in lipoprotein metabolism, such as familial hypercholesterolemia.
Some one asked George Bernard Shaw: “what is the secret for a healthy life?”
George Bernard Shaw replied: “Select your parents carefully”
Hyperlipidemia

Hyperlipidemia (more specifically Hypercholestrolemia) is the strongest risk factor for atherosclerosis.

Components of plasma lipids associated with increased risk of ISD:

1. Increased Cholesterol
2. Increased Low Density Lipoprotein (LDL)
3. Low High Density Lipoprotein (LDL)
4. High Very Low Density Lipoprotein (VLDL)
1. **Cholesterol**:
- Less than 200 mg/dl - Desirable
- 200 mg/dl – 239 mg/dl – Borderline
- More than 240 mg/dl - High Risk

2. **Low Density Lipoprotein (LDL)**:
   LDL has high content of cholesterol. It is greatly increased in familial hypercholesterolemia. Serum LDL level more than 160 mg/dl increases the risk of atherosclerosis.

3. **Total plasma Triglycerides**:
   A level of more than 250 mg/dl imposes a high risk

4. **High Density Lipoprotein (HDL) cholesterol ("Good Cholesterol")**:
   This is a protective lipoprotein. Low level of HDL increases risk of atherosclerosis. HDL less than 35 mg/dl imposes a high risk
   - HDL cholesterol mobilizes cholesterol from developing and existing vascular plaques and transports it to liver for biliary excretion

5. **Very Low Density Lipoprotein (VLDL)**:
   VLDL is rich in triglyceride. High levels of VLDL is also associated with some increased risk of atherosclerosis
Genetic defects in lipoprotein metabolism causing hyperlipoproteinemia are associated with accelerated atherosclerosis

<table>
<thead>
<tr>
<th>Electrophoretic Phenotype</th>
<th>Increased Lipoprotein Class(es)</th>
<th>Increased Lipid Class(es)</th>
<th>Relative Frequency (%)</th>
<th>Known Underlying Genetic Defects</th>
<th>Atherogeneticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Triglycerides</td>
<td>&lt;1</td>
<td>Mutation in lipoprotein lipase gene</td>
<td>None</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>Cholesterol</td>
<td>10</td>
<td>Mutation in LDL receptor gene or in apolipoprotein B gene</td>
<td>+++</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL &amp; VLDL</td>
<td>Cholesterol &amp; Triglycerides</td>
<td>40</td>
<td>Mutation in LDL receptor gene or in lipoprotein B gene</td>
<td>+++</td>
</tr>
<tr>
<td>III</td>
<td>Remnants (chylomicrons and IDL)</td>
<td>Triglycerides &amp; Cholesterol</td>
<td>&lt;1</td>
<td>Mutation in apoprotein E gene</td>
<td>+++</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Triglycerides</td>
<td>45</td>
<td>Mutation in lipoprotein lipase gene</td>
<td>+</td>
</tr>
<tr>
<td>V</td>
<td>VLDL &amp; chylomicrons</td>
<td>Triglycerides &amp; cholesterol</td>
<td>5</td>
<td>Mutation in apolipoprotein gene</td>
<td>+</td>
</tr>
</tbody>
</table>
Hypertension

- Both Systolic and Diastolic levels are important in increasing risk. Important risk factor in people 45 years of age

- Atherosclerosis is five times more common in an individual whose blood pressure is more than 160/95 than those whose
Estimated 10 years risk of coronary artery disease in hypothetical 55 years old man and woman as a function of traditional risk factors
Cigarette Smoking

- When one or more packs of cigarettes are smoked per day for several years, the death rate from ischemic heart disease increases by up to 200%.

- Cessation of smoking approximately halves this increased risk.
How to have healthy and wiser life?

While doing anything if you find fun in it, just don’t do it!!!!
Diabetes Mellitus

- Diabetes Mellitus induces hypercholesterolemia and a markedly increased predisposition to atherosclerosis

- There is also an increased risk of:
  - Stroke
  - Atherosclerosis – induced gangrene of the lower extremities
Additional Risk Factors for IHD

- As many as 20% of all cardiovascular events occur in the absence of any of the major risk factors.

- Indeed, even though hyperlipidemia is clearly contributory, more than 75% of cardiovascular events in previously healthy women occurred with LDL cholesterol levels below 160 mg/dl (a cutoff generally considered to suggest low risk).

- Clearly, other “nontraditional” factors contribute to risk.
Inflammation as marked by C-Reactive Protein

- Inflammation is present during all stages of atherogenesis and is intimately linked with atherosclerotic plaque formation and rupture.

- With the increasing recognition that inflammation does play a significant role in ischemic heart disease (IHD), assessing systemic inflammatory status has become important in overall risk stratification.

- While a number of systemic markers of inflammation correlate with IHD, CRP has emerged as one of the cheapest and most sensitive.
CRP adds prognostic information at all levels of traditional risk. Relative risk (y-axis) refers to the risk of a cardiovascular event (e.g., Myocardial infarction). The x-axis is the 10 years risk of a cardiovascular event derived from the traditional risk factors.
Hyperhomocysteinemia

- Clinical and epidemiologic studies show a strong relationship between total serum homocysteine levels and:
  - Coronary artery disease
  - Peripheral vascular disease
  - Stroke
  - Venous thrombosis
  - Neural tube defects in fetus

- There is evidence that homocysteine may cause endothelial dysfunction, through formation of reactive oxygen species, which eventually plays an important role in atherosclerosis.

- Elevated homocysteine levels can be caused by low folate and Vitamin B12 intake.
  - But

- The jury is still out on whether supplemental folate and Vitamin B6 ingestion can reduce the incidence of CVS disease.

- Homocystinuria: A rare inborn error of metabolism, resulting in high circulating levels of homocysteine.
Lipoprotein a

- It is an altered form of LDL
- Increased levels of Lipoprotein a are associated with higher risk of coronary artery and cerebrovascular disease
Factors Effecting Hemostasis

Several markers of hemostasis and/or fibrinolytic function (e.g., elevated plasminogen activator inhibitor 1) are strong predictors of risk for major atherosclerotic events.
The overwhelming clinical importance of atherosclerosis has stimulated enormous efforts to understand its cause.

Histologically there are two dominant theories:
(1) Intimal cellular proliferation in response to endothelial injury
(ii) Repeated formation and organization of thrombus

The contemporary view of atherogenesis incorporates elements of both theories and also integrates the risk factors.

The contemporary view of atherogenesis is expressed by the **RESPONSE – TO INJURY HYPOTHESIS**.
This model views *atherosclerosis as a chronic inflammatory response to endothelial injury*. Lesion progression occurs through interactions of modified lipoproteins, monocyte-derived macrophages, T-lymphocytes and the normal cellular constituents of the arterial wall.
Central Tenets of the Response – To –Injury Hypothesis

Following are central tenets of the hypothesis:

1. **Chronic Endothelial Injury**, with resultant endothelial dysfunction, causing (among other things) increased permeability, leucocyte adhesion and thrombosis

2. **Accumulation of Lipoproteins** mainly LDL and its oxidized forms, in the vessel wall

3. **Monocyte Adhesion to the Endothelium**, followed by migration into intima and transformation into macrophages and **foam cells**

4. **Platelet Adhesion**

5. **Factors Release** from activated platelets, macrophages, and vascular wall cells, inducing smooth muscle cell recruitment, either from the media or from circulating precursors

6. **Smooth Muscle Cells Proliferation** and **Extracellular Matrix Production**

7. **Lipid Accumulation** both extracellular and within cells (macrophages and smooth muscle cells)
The accumulation of lipid-containing macrophages in the intima gives rise to "FATTY STREAKS". With further evolution, a FIBROFATTY ATEROMA consisting of proliferated smooth muscle cells, foam cells, extracellular lipid and extracellular matrix is formed.
Formation of Foam Cells

- Foam cells of atheromatous plaques are derived from both macrophages and smooth muscle cells
  - From Macrophages via the very-low-density-lipoprotein (VLDL) receptor and low-density-lipoprotein (LDL) modifications recognized by scavenger receptors (e.g., oxidized LDL)
  - From Smooth Muscle Cells by less uncertain mechanisms
Evolution of Arterial Wall Changes in the Response To Injury Hypothesis

1. Normal

2. Endothelial injury with adhesion of monocytes and platelets (platelets adhere to sites where endothelium has been lost)

3. Migration of monocytes and smooth muscle cells into intima

4. Smooth muscle cells proliferation in the intima with extracellular matrix elaboration

5. Well developed plaque
Endothelial Injury

- Chronic or reparative endothelial injury is the cornerstone of the response-to-injury hypothesis.

- In the presence of high lipid diets, typical atheroma ensues.

- However, early human lesions begin at sites of morphologically intact endothelium.

- Thus non-denuding endothelial dysfunction underlies human atherosclerosis.

- In the setting of intact but dysfunctional endothelial cells there is increased endothelial permeability, enhanced leucocyte adhesion and altered gene expression.

- The **important causes of endothelial dysfunction:**
  1. Haemodynamic Disturbances
  2. Hypercholesterolemia
  3. Inflammation
  4. Infections
The importance of haemodynamic factors in atherogenesis is well illustrated by occurrence of atheromatous plaques at sites of turbulent blood flow.

Repeated episodes of mural thrombosis and organization leads to the progressive build up of elevated plaques.

Lipid content could be derived from breakdown of platelets, leucocytes and erythrocytes.
Role of Lipids in Endothelial Injury

Lipids are typically transported in the bloodstream bound to specific apoproteins (*forming lipoprotein complexes*).

**Major pathways of lipoprotein metabolism:**
- LDL uptake in peripheral tissues is receptor-mediated. HDL accepts cholesterol from tissues. This can be absorbed by specific receptors in the liver (reverse cholesterol transport) or recycled into LDL.
Dyslipoproteinemias can result from:
1. Mutations that encode defective apoproteins
2. Mutations that alter the lipoprotein receptors on cells.
3. Some underlying disorder that affects the circulating levels of lipids, e.g.:
   - Nephrotic Syndrome
   - Alcoholism
   - Hypothyroidism
   - Diabetes Mellitus

Common Lipoprotein Abnormalities include:
(i) Increased LDL cholesterol levels
(ii) Decreased HDL cholesterol levels
(iii) Increased levels of abnormal Lipoprotein (a)

Epidemiologic studies like famous Framingham study demonstrates a significant correlation between the severity of atherosclerosis and the levels of total plasma cholesterol or LDL
How Hyperlipidemia Contributes to Atherogenesis

- Hypercholesteroolemia impair endothelial cell function by increasing local production of reactive oxygen species.

- Lipoproteins accumulated in intima are oxidized through action of oxygen derived free radicals, which are generated locally by macrophages or endothelial cells.

- Oxidized LDL is ingested by macrophages through a Scavenger Receptor, resulting in foam cell formation.

- Oxidized LDL stimulates the release of growth factors, cytokines and chemokines by endothelial cells and macrophages that increase monocyte recruitment into lesions.

- Oxidized LDL is cytotoxic to endothelial cells and smooth muscle cells and can induce endothelial cells dysfunction.
**Role of Inflammation in Endothelial Injury**

- Inflammatory cells and mediators are involved in the initiation, progression and the complications of atherosclerotic lesions.
- After the inflammatory cells adhere to endothelium they migrate into intima under the influence of locally produced chemokines.

**Role of Monocytes in Endothelial Injury**

- Monocytes transform into macrophages and avidly engulf lipoproteins, including oxidized LDL.
- Monocytes recruitment and differentiation into macrophages and ultimately into foam cells is theoretically protective, since these cells remove potentially harmful lipid particles. Over the time, however progressive accumulation of oxidized LDL drives lesion progression.
- Activated macrophages produce cytokines and reactive oxygen species, aggravating LDL oxidation.
Role of T Lymphocytes in Endothelial Injury

- T- Lymphocytes recruited to the intima interact with macrophages and can generate a chronic immune inflammatory state.

As a result of the chronic inflammatory state, activated leucocytes and vascular wall cells release growth factors that promote smooth muscle cells proliferation and extracellular matrix synthesis.
Role of Infections in Endothelial Injury

- Herpes virus, cytomegalovirus and Chlamydia Pneumonia have all been detected in atherosclerotic plaque.

- A causal link between any of these infections and the development or progression of atherosclerosis remains to be established.
Intimal smooth muscle proliferation and extracellular matrix deposition convert a fatty streak into a mature atheroma and contributes to the progressive growth of atherosclerotic lesions.

Intimal smooth muscle cells have a proliferative and synthetic phenotype distinct from the underlying medial smooth muscle cells.

Different growth factors play an important role in the smooth muscle cells proliferation:
- Platelet-derived growth factor
- Fibroblast growth factor
- Transforming growth factor alpha
Stages of atherosclerotic plaque development
Major Proposed Cellular Mechanisms of Atherogenesis

- Arthrosclerosis is a disease of multifactorial pathogenesis
- Atherosclerosis is a chronic inflammatory response of the vascular wall to a variety of insults, including endothelial injury, lipid accumulation, and oxidation and thrombosis.
- Atheromas are dynamic lesions consisting of dysfunctional endothelial cells, recruited and proliferating smooth muscle cells and admixed chronic inflammation (macrophages and lymphocytes)
- All four cell types (endothelial cells, smooth muscle cells, macrophages and lymphocytes) contribute mediators that influence atherogenesis
- At early stages, intimal plaques are little more than aggregates of macrophages and smooth muscle cells foam cells, some of which die, releasing lipid and necrotic debris
With progression, the atheroma is modified by collagen and proteoglycans synthesized by smooth muscle cells.

Connective tissue is particularly prominent on the intimal aspect, producing a fibrous cap.

Lesions typically retain a central core of lipid–laden cells and fatty debris that may also become calcified over time.

Disruption of the fibrous cap with superimposed thrombus is often associated with catastrophic clinical events.
Hypothetical sequence of cellular interactions in atherosclerosis:

- Hyperlipidemia and other risk factors are thought to cause endothelial injury, resulting in adhesion of platelets and monocytes and release of growth factors, including platelet-derived growth factor, which lead to smooth muscle cells migration and proliferation.
- Foam cells of atheromatous plaques are derived from both macrophages and smooth muscle cells.
- Extracellular lipid is derived from insudation from the vessel lumen, particularly in the presence of hypercholesterolemia, and also from degenerating foam cells.
- Cholesterol accumulation in the plaque reflects an imbalance between influx and efflux, and high-density lipoprotein (HDL) probably helps clear cholesterol from these accumulations.
- Smooth muscle cells migrate to the intima, proliferate and produce extracellular matrix, including collagen and proteoglycans.
Haemodynamic Disturbances

Hypercholesterolemia

Inflammation

Infection

ENDOTHELIAL INJURY

Intact but dysfunctional endothelium; Increased endothelial permeability; Enhanced leucocytes adhesion; Altered gene expression

Adhesion of Monocytes and Platelets

Migration of monocytes and smooth muscle muscles into intima

Proliferation of smooth muscle cells in intima with extracellular matrix elaboration

Macrophages with Cholesterol (Foam Cells)

Formation of Fatty Streaks in blood vessels

Formation of Fibrofatty Atheroma

Well Developed Plaque

Atherosclerosis

Ischemia

Ischemic Heart Disease; Cerebral Infarction; Gangrene; Peripheral Vascular Disease; Transient Ischemic Attacks
Atherosclerosis- Morphology

Two Morphologic Lesions in Atherosclerosis:

1. Fatty Streak

2. Atheromatous Plaque
**Fatty Streak**

- Fatty Streaks are composed of lipid-filled foam cells but are not significantly raised and thus do not cause any disturbance in blood flow.

- They start as multiple minute yellow, flat spots that can coalesce into elongated streaks.

- Fatty streaks can appear in the aortas of infants younger than 1 year and are present in virtually all children older than 10 years, regardless of geography, race, sex or environment.

- Coronary fatty streaks begin to form in adolescence, at the same anatomic sites that later tend to develop plaques.

- The relationship of fatty streaks to atherosclerotic plaques is uncertain; although they may evolve into precursors of plaques, not all fatty streaks are destined to become advanced atherosclerotic lesions.
The key processes in atherosclerosis are intimal thickening and lipid accumulation.

Atheromatous plaques (also called fibrous or fibrofatty plaques) impinge on the lumen of the artery and grossly appear white to yellow.

Thrombosis superimposed over the surface of ulcerated plaque is red-brown in colour.

Plaques can coalesce to form larger masses.

Atherosclerotic lesions are patchy, usually involving only a portion of any given arterial wall. On cross section the lesions therefore appear “eccentric.”

Local flow disturbances, such as turbulence at branch points, leads to certain portions of a vessel wall being more susceptible to plaque formation.

Over the time the lesions become more diffuse and numerous.
Lesions of Atherosclerosis

A: Early aortic atherosclerosis. Note the many small fatty streaks. Some larger-dot-like lesions are also present. These are common lesions in all racial groups and both genders.

B: Advanced complicated atherosclerosis in the abdominal aorta. Many of the lesions have ruptured and become thrombosed.
**A:** Mild atherosclerosis composed of fibrous plaque (arrow)

**B:** Severe Atherosclerosis with diffuse and complicated lesions, some of which have coalesced
Fatty Streak- A Collection of Foam Cells in Intima

A: Aorta with fatty steaks (arrows)
B: Photomicrograph of fatty streak in an experimental rabbit, demonstrating intimal, macrophage-derived foam cells (arrows)
A: Overall architecture demonstrating fibrous cap (F) and a central necrotic core (C). The lumen (L) has been moderately narrowed. Note that a segment of the wall is plaque free (arrow).

B: Elastin stain (black) demonstrating the internal and external elastic membranes. These are destroyed and the media of the artery is thinned under the most advanced plaque (Arrow).

C: Junction of the fibrous cap and core, showing scattered inflammatory cells, calcification (arrow head) and neovascularization (small arrow).
A: Plaque rupture (arrow) without superimposed thrombus, in a patient who died suddenly

B: Acute coronary thrombosis superimposed on an atherosclerotic plaque with focal disruption of the fibrous cap (arrow), triggering fatal myocardial infarction
Mild, Moderate, Severe Atherosclerosis
This is a high magnification of the aortic atheroma with foam cells and cholesterol clefts.
Atheromatous Plaque
The Commonly Involved Arteries in the Process of Atherosclerosis

- Lower Abdominal Aorta
- Coronary Arteries
- Popliteal Arteries
- Internal Carotid Arteries
- Vessels of Circle of Willis
Three Principal Components of Atherosclerotic Plaque

(1) Cells, including:
   - Smooth Muscle Cells
   - Macrophages
   - T- Lymphocytes

(2) Extracellular Matrix, including:
   - Collagen
   - Elastic Fibers
   - Proteoglycans

(3) Intracellular and Extracellular Lipids
At the periphery of the lesions, there is usually “Neovascularization.”

Plaques generally continue to change and progressively enlarge through cell death and degeneration,

Atheroma often undergo Calcification. Patients with advanced coronary calcification appear to be at increased risk for coronary events.
Clinically Significant Changes in Atherosclerotic Plaque

1. **Rupture, Ulceration, or Erosion of the luminal surface of atheromatous plaques**
   - It exposes the blood stream to highly thrombogenic substances and induces thrombus formation.
   - Such thrombi can partially or completely occlude the lumen and lead to downstream ischemia (i.e., in the heart).

2. **Haemorrhage into plaque**
   - Rupture of the overlying fibrous cap of the thin-walled vessels in the areas of neovascularization can cause intra-plaque haemorrhage.
   - A contained haematoma may expand the plaque or induce plaque rupture.

3. **Atheroembolism**
   - Plaque rupture can discharge debris into the bloodstream, producing microemboli composed of plaque contents.

4. **Aneurysm Formation**
   - Atherosclerosis-induced pressure or ischemic atrophy of the underlying media, with loss of elastic tissue, causes weakness of the vessel wall and development of aneurysms that may rupture.
Natural History of Atherosclerosis

- Atherosclerosis primarily affects: **Elastic Arteries** for example aorta, carotid and Iliac arteries
  **Large and Medium Sized Arteries** like Coronary and Popliteal
  In **small arteries**, atheroma can gradually occlude lumina, compromising blood flow to distal organs and cause ischemic injury

- Atherosclerotic plaques can undergo acute 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 can rupture.

- Atheromas can be friable, fragmenting atheroemboli into downstream circulation
The Natural History, Morphologic Features, Main Pathologic Events and Clinical Complications of Atherosclerosis
<table>
<thead>
<tr>
<th>Nomenclature and main histology</th>
<th>Sequences in progression</th>
<th>Main growth mechanism</th>
<th>Earliest onset</th>
<th>Clinical correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (initial) lesion</td>
<td>I</td>
<td>Growth mainly by lipid accumulation</td>
<td>From first decade</td>
<td>Clinically silent</td>
</tr>
<tr>
<td>Isolated macrophage foam cells</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II (fatty streak) lesion</td>
<td>II</td>
<td>Accelerated smooth muscle and collagen increase</td>
<td>From third decade</td>
<td></td>
</tr>
<tr>
<td>Mainly intracellular lipid accumulation</td>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type III (intermediate) lesion</td>
<td>III</td>
<td>Thrombosis, hematoma</td>
<td>From fourth decade</td>
<td>Clinically silent or overt</td>
</tr>
<tr>
<td>Type IV (atheroma) lesion</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II changes and core of extracellular lipid</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type V (fibroatheroma) lesion</td>
<td>V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific, or mainly fibrotic</td>
<td>V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type VI (complicated) lesion</td>
<td>VI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surface defect, hematoma-hemorrhage, thrombus</td>
<td>VI</td>
<td></td>
<td></td>
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</tbody>
</table>

American Heart Association Classification of Human Atherosclerotic Lesions From the Fatty Dot (Type I) to the Complicated Lesion (Type VI)

The diagram also includes growth mechanisms and clinical correlations.
Atherosclerosis is a slowly evolving lesion usually requiring many decades to become significant

**HOWEVER**

- Acute plaque changes (e.g., Rupture, Thrombosis or Haematoma) can rapidly precipitate clinical sequelae (the so-called “Clinical Horizon”)

- Symptomatic atherosclerotic disease most often involves the arteries supplying the heart, brain, kidneys and lower extremities
Major Consequences of Atherosclerosis

- Myocardial Infarction (Heart Attack)
- Cerebral Infarction (Stroke)
- Aortic Aneurysms
- Peripheral Vascular Disease (Gangrene of the legs)
Atherosclerosis also takes a toll through other consequences of acutely or chronically diminished arterial perfusion, such as:
- Mesenteric Occlusion
- Sudden Cardiac Death
- Chronic Ischemic Heart Disease
- Ischemic Encephalopathy

The effects of vascular occlusion ultimately depend on:
- Arterial Supply
- Tissue Metabolic Demand
Plaques usually develop slowly and insidiously over many years, beginning in childhood or shortly thereafter. May progress from a fatty streak to a fibrous plaque and then to a complicated plaque that is likely to lead to clinical effects.
Prevention of Atherosclerotic Vascular Disease

**Primary Prevention Programmes**

- Aimed at either delaying atheroma formation or encouraging regression of established lesions in persons who have not yet suffered a serious complication of atherosclerosis

- It involves factor identification and modification of those factors which are amenable to intervention, like:
  - Cessation of Cigarette Smoking
  - Control of Hypertension
  - Weight Loss
  - Exercise
  - Lowering of total and LDL Cholesterol levels and increasing HDL levels (by diet or through statins)
Secondary Prevention Programmes

- Intended to prevent recurrence of events such as myocardial infarction or stroke in symptomatic patients

- It involves:
  - Judicious use of aspirin (anti-platelet agent), statins, and beta blockers (to limit cardiac demand)
  - Surgical Intervention (Coronary Artery Surgery, Carotid Endarterectomy)
Three Main Contributors of Improvement

(1) Prevention of atherosclerosis through recognition of risk factors and change in life style (e.g., reduced cigarette smoking, reduced consumption of cholesterol and control of hypertension

(2) Improved methods of treatment myocardial infarction and other complications of ischemic heart disease

(3) Prevention of recurrences in patients who have previously suffered atherosclerosis-related clinical events
## Summary: Atherosclerosis

<table>
<thead>
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<th><strong>Atherosclerosis</strong></th>
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<td>Atherosclerosis is an intima based lesion composed of a fibrous cap and an athermanous core; the constituents of the plaque include smooth muscle cells, ECMs, inflammatory cells, lipids and necrotic cells.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Atherogenesis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherogenesis is driven by an interplay of vessel wall injury and inflammation. The multiple risk factors for atherosclerosis all cause endothelial cell dysfunction and influence smooth muscle cell recruitment and stimulation.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th><strong>Atherosclerotic plaques</strong></th>
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<tr>
<td>Atherosclerotic plaques develop and grow slowly over decades. Stable plaques can produce symptoms related to chronic ischemia by narrowing vessels, whereas unstable plaques can cause dramatic and potentially fatal ischemic complications related to acute plaque rupture, thrombosis or embolization.</td>
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<table>
<thead>
<tr>
<th><strong>Stable plaques</strong></th>
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<tbody>
<tr>
<td>Stable plaques tend to have a dense fibrous cap, minimal lipid accumulation, and little inflammation, whereas “vulnerable” unstable plaques have thin caps, large lipid cores and relatively dense inflammatory infiltrates.</td>
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</table>
## Stable Vs Unstable Plaques

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<th>Unstable Plaque</th>
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Diseases of Blood Vessels

HYPERTENSION
Hypertension

- Systemic and local blood pressures must be tightly regulated.
- Low blood pressures result in inadequate organ perfusion, leading to dysfunction and/or tissue death.
- High Blood Pressure (Hypertension) drive blood flow in excess of metabolic demands, providing no additional benefit but result in blood vessel and end-organ damage.
- Hypertension remains asymptomatic until late in its course.
- Hypertension can lead to
  - Atherosclerosis
  - Cerbrovascular accidents
  - Cardiac Hypertrophy
  - Heart Failure
  - Aortic Dissection
  - Renal Failure
A sustained diastolic pressure greater than 90 mm of Hg

OR

A sustained systolic pressure in excess of 140 mm of Hg
Constitutes Hypertension

Systolic blood pressure is more important in determining cardiovascular risk
Regulation of Blood Pressure

- Blood pressure is a complex trait involving the interaction of multiple genetic and environmental factors that influence two hemodynamic variables:
  1. Cardiac Output
  2. Peripheral Vascular Resistance

- Two central players in Blood Pressure regulation:
  1. Kidneys (primarily)
  2. Adrenals (Secondarily)

- The kidneys and adrenals interact with each other to modify vessel tone and blood volume
Blood pressure modulation by effects on cardiac output and peripheral resistance
The kidney influence peripheral resistance and sodium homoeostasis primarily through the **Renin-Angiotensin System**.

When blood volume or pressure is reduced, the kidney senses this as a decreased pressure in the afferent arterioles. Lower volumes or pressures result in a reduced **Glomerular Filtration Rate** in the kidney with **increased Resorption of Sodium** by proximal tubules; these latter two effects conserve sodium and expand the blood volume.

The juxtaglomerular cells respond to reduced intra-luminal pressures in the afferent arterioles by releasing renin.

**Blood pressure modulation by effects on cardiac output and peripheral resistance**
Role of Kidney in Blood Pressure Regulation

Renin catabolizes plasma **Angiotensinogen** to **Angiotensin I**, which is converted to **Angiotensin II** by **Angiotensin-Converting Enzyme** in the periphery.

Angiotensin II raises blood pressure by:
1. Increasing peripheral resistance by inducing vascular smooth muscle cells contraction
2. Increasing blood volume by stimulating aldosterone secretion in the adrenals
3. Increasing distal tubular reabsorption of sodium
Components of the systemic renin-angiotensin system are shown in black. Some genetic disorders that affect blood pressure by altering activity of this pathway are indicated in red; arrows indicate sites in the pathway altered by mutation. Acquired disorders that alter blood pressure through effects on this pathway are indicated in green.
# Types and Causes of Hypertension (Systolic and Diastolic)

## I. ESSENTIAL HYPERTENSION (90 to 95% of cases)

## II. SECONDARY HYPERTENSION

### RENAL
- Acute Glomerulonephritis
- Chronic Renal Disease
- Polycystic Disease
- Renal Artery Stenosis
- Renal Vasculitis
- Renin-producing tumours

### CARDIOVASCULAR
- Coarctation of Aorta
- Polyarteritis Nodosa
- Increased Intravascular Volume
- Increased Cardiac Output
- Rigidity of Aorta

### NEUROLOGIC
- Psychogenic
- Increased Intracranial Pressure
- Sleep Apnea
- Acute Stress, including Surgery

### ENDOCRINE
- Adrenocortical Hyperfunction
  - Cushing Syndrome
  - Primary Aldosteronism
  - Congenital Adrenal Hyperplasia
  - Licorice Ingestion
- Exogenous Hormones
  - Glucocorticoids; Estrogens (including pregnancy induced and oral contraceptives)
- Sympathomimetiscs & Tyramine-containing foods
- Monoamine Oxidase Inhibitors
- Pheochromocytoma
- Hypothyroidism (Myxedema)
- Hypertthyroidism (Thyrotoxicosis)
- Pregnancy induced
Pathogenesis of Hypertension

Ninety percent to 95% of hypertension is idiopathic (*Essential Hypertension*)

- Essential Hypertension is compatible with long life, unless a myocardial infarction, cerebrovascular accident or other complications supervenes.

- Most of the remainder of “Benign Hypertension” is secondary to renal disease or less often to narrowing of the renal artery, usually by an Atheromatous plaque (*renovascular hypertension*).

- Infrequently, hypertension is secondary to diseases of the adrenal glands, such as primary aldosteronism, Cushing syndrome, Pheochromocytoma or other disorders.
Accelerated OR Malignant Hypertension:

- About 5% of hypertensive persons show a rapidly rising blood pressure that if untreated leads to death within 1 or 2 years.

- Malignant Hypertension is characterized by severe hypertension (diastolic pressure over 120mg Hg), renal failure, and retinal haemorrhages and exudates, with or without papilledema.

- It may develop in previously normotensive persons but more often is superimposed on preexisting benign hypertension, either essential or secondary.
Pathogenesis of Essential Hypertension

1. Reduced Renal Sodium Excretion
2. Alterations in Vascular Tone
3. Genetic Factors
4. Environmental factors
Reduced renal sodium excretion in the presence of normal arterial pressure is probably a key initiating event.

It is the final common pathway for the pathogenesis of most forms of hypertension.

Decreased sodium excretion will cause an obligatory increase in fluid volume and increased cardiac output, thereby elevating blood pressure.
Vascular Changes

- Vascular changes may involve functional vasoconstriction or changes in vascular wall resistance that result in increased resistance.

Although we frequently cannot point to a discrete cause, the accepted wisdom is that essential hypertension results from an interplay of multiple genetic and environmental factors affecting cardiac output and/or peripheral resistance.
Hypothetical scheme for the pathogenesis of essential hypertension, implicating genetic defects, defects in regulation of vascular tone, and structural regulation of vascular caliber. Environmental factors, especially increased salt intake, potentiate the effects of genetic factors. The resultant increase in cardiac output and peripheral resistance contributes to hypertension.
Genetic Factors

- Studies comparing blood pressure in monozygotic twins and studies of familial clustering of hypertension, clearly establish a strong genetic component

- Allelic variations in the genes encoding components of the renin–angiotensin system may contribute
Environmental Factors

- Environmental factors modify the expression of any underlying genetic determinant of hypertension.

- Stress, obesity, smoking, physical inactivity and heavy consumption of salt are all implicated.
Morphologic Changes in Hypertension

Morphologically, hypertension is associated with two forms of small blood vessel disease:

1. Hyaline Arteriolarosclerosis

2. Hyperplastic Arteriolarosclerosis
Hyaline Arteriolosclerosis

- This vascular lesion consists of a homogenous pink hyaline thickening of the walls of arterioles with loss of underlying structural detail and with narrowing of the lumen.

- In addition to Hypertension also seen in Diabetic Microangiopathy.
Hyaline Arteriosclerosis: The arteriolar wall is hyalinized and the lumen is markedly narrowed.
HYALINE ARTERIOLOSCLEROSIS

- Normal glomerulus
- Partial hyalinization of a glomerulus
- Hyalinization within arterial wall
- Tubules
- Total hyalinization of a glomerulus
Hyperplastic Arteriolosclerosis

- Related to more acute or severe elevations of blood pressure.
- It is characteristic of Malignant Hypertension.
- Hyperplastic arteriolosclerosis is associated with "Onion-Skin", concentric laminated thickening of the walls of arterioles with luminal narrowing.
- The laminations consist of smooth muscle cells and thickened duplicated basement membrane.
- In malignant hypertension these hyperplastic changes are accompanied by fibrinoid deposits and vessel wall necrosis (Necrotizing Arteriolitis), particularly prominent in kidneys.
Hyperplastic Arteriolosclerosis (onion-skinning) causing luminal obliteration (arrow) with secondary ischemic changes, manifest by wrinkling of the glomerular capillary vessels at the upper part left.
HYPERPLASTIC ARTERIOLOOSCLEROSIS
There are two other forms of arteriosclerosis (hardening of the arteries) in addition to atherosclerosis: arteriolosclerosis and medial calcific sclerosis. Arteriolosclerosis is typically seen in the kidneys. One form, called hyaline arteriolosclerosis, is demonstrated by the markedly thickened arteriole to the lower right of this glomerulus with PAS stain. Hyaline arteriolosclerosis is seen in the elderly, but more advanced lesions are seen in persons with diabetes mellitus and/or with hypertension.
One complication of hyperplastic arteriolosclerosis with malignant hypertension is fibrinoid necrosis, as seen here in a renal arteriole.
# Summary: Hypertension

<table>
<thead>
<tr>
<th>Hypertension</th>
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<tbody>
<tr>
<td>Hypertension is a common disorder affecting 25% of the population; It is a major risk factor for atherosclerosis, congestive heart failure and renal failure</td>
</tr>
<tr>
<td>Essential hypertension represents 95% of cases and is a complex, multi-factorial disorder, involving both environmental influences and genetic polymorphisms that may influence sodium resorption, aldosterone pathways and the renin-angiotensin system</td>
</tr>
<tr>
<td>Hypertension occasionally is caused by single-gene disorders or is secondary to diseases of the kidney, adrenal or other endocrine organs</td>
</tr>
</tbody>
</table>
Diseases of Blood Vessels

ANEURYSMS & DISSECTIONS
ANEURYSMS & DILATATIONS

ANEURYSM

- An aneurysm is a localized abnormal dilatation of a blood vessel wall.
- **True Aneurysm**: An aneurysm involving all three layers of arterial wall (intima, media, and adventitia) OR the attenuated wall of the heart.
- **Pseudo (False) Aneurysm**: It is a breach in the vascular wall leading to an extra vascular hematoma that freely communicates with the intravascular space ("pulsating hematoma").

DISSECTION

- An arterial dissection arises when blood enters the wall of the artery, as a hematoma dissecting between its layers.
## True VS False Aneurysm

<table>
<thead>
<tr>
<th>True Aneurysm</th>
<th>False Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>True aneurysm is a permanent dilatation of a part of the vascular tree</td>
<td>False aneurysm is a blood-filled space that forms around a blood vessel, usually after traumatic rupture or a perforating injury</td>
</tr>
<tr>
<td>Permanent dilatation implies that the vessels wall has been weakened</td>
<td>A hematoma forms and is contained by the adventitial fibrous tissue</td>
</tr>
<tr>
<td>A common cause of false aneurysm is <strong>FEMORAL ARTERY PUNCTURE</strong> during arteriography or percutaneous angioplasty</td>
<td></td>
</tr>
</tbody>
</table>
A: Normal vessel

B: True Aneurysm, saccular type. The wall focally bulges outward and may be attenuated but is otherwise intact

C: True aneurysm, fusiform type. There is circumferential dilatation of the vessel, without rupture

D: Pseudo (False) anerysm. The wall is ruptured and there is a collection of blood (hematoma) that is bounded externally by adherent extravascular tissues

E: Dissection. Blood has entered (dissected) that wall of the vessel and separated the layers. Although this is showing as occuring through a tear in the lumen, dissection can also occur by rupture of the vessels of the vaso vasorum within the media
Aneurysms and dissections result from structural weakness of the vessel wall caused by loss of smooth muscle cells or insufficient extracellular matrix which can be a consequence of ischemia, genetic defects or defective matrix remodeling.
Types of Aneurysms - AN OVERSIMPLIFICATION(!)

1) On the basis of development

2) On the basis of Appearance

3) True Aneurysms - Sub types
Aneurysms – On the basis of Development

1) True Aneurysm

2) Pseudo (False) Aneurysm
Aneurysms – On the basis of Appearance

1) Saccular

2) Fusiform
Saccular Aneurysm

Fusiform Aneurysm

Ruptured Aneurysm
True Aneurysms – Subtypes

1) Atherosclerotic
2) Dissecting
3) Berry
4) Capillary
5) Syphilitic
6) Mycotic
Atherosclerotic Aneurysm

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

These intimal 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 dilatation of the vessel.

Aneurysm is formed.
Atherosclerotic Aneurysm.... contd

- Atherosclerotic aneurysms occur more frequently in the abdominal aorta *(Abdominal Aortic Aneurysm; AAA)*.

- Common iliac arteries, the arch and descending parts of the thoracic aorta can also be involved.

- Abdominal Aortic Aneurysm results from an altered balance of collagen degradation and synthesis mediated by local inflammatory infiltrates and the destructive proteolytic enzymes they produce and regulate.

- Thus, abnormal collagen or elastic tissue—or inadequate remodeling of these extracellular matrix components provide a background on which atherosclerosis or hypertension weaken the aortic wall.
ABDOMINAL AORTIC ANEURYSMS (AAA):

- Atherosclerosis
- > 50 yrs
- > males, smokers
- genetic susceptibility $\rightarrow$ connective tissue strength

MMP $\Leftrightarrow$ TIMP

HTN
Role of Matrix Metalloproteinases (MMP)

Metalloproteinases are expressed in aortic aneurysms at elevated levels compared with the normal vessel wall.

- Production of Cytokines (IL-4 and IL-10)
- Stimulation of Macrophages
- Production of increased amounts of Matrix Metalloproteinases
- Degradation of all components of extracellular matrix in the arterial wall (Collagens, Elastin, Proteoglycan, Laminin, Fibronectin)
**Abdominal Aortic Aneurysm**

**A**: External view, gross photograph of a large aortic aneurysm that ruptured (arrow)

**B**: Opened view, with the location of the rupture tract indicated by a probe. The wall of the aneurysm is exceedingly thin, and the lumen is filled by a largely unorganized thrombus
Atherosclerotic Abdominal Aortic Aneurysm

- This large aneurysm was an incidental finding at postmortem.

- Screening by ultrasound may detect these aneurysms in life.
Aortic Aneurysm
Aortic Aneurysm
Atherosclerosis
(Abdominal aorta)

Hypertension
(ascending aorta)

Aneurysm
# Aortic Aneurysm - Summary

## Aortic Aneurysm

### Etiology and Epidemiology
Associated with Atherosclerosis, CAD and Trauma.; Familial predisposition and cystic medial necrosis; Occurs most frequently in men aged>50 years

### Pathology
Artery: Most commonly found in the descending aorta below the renal arteries although occurs in thoracic aorta as well; occurs in areas of wall thickening (Atherosclerotic plaque can destroy media) or in localized dilatations of arteries and veins; saccular out pouching often filled with atherosclerotic plaque or thrombus

### Clinical Manifestations
Usually asymptomatic until rupture; abdominal aortic aneurysm (AAA) may present with pulsating, painless upper abdominal mass; if ruptured, AAA will present with severe tearing abdominal pain radiating to the back and hypotension. Patients with ascending thoracic aneurysms may develop aortic insufficiency or have chest pain; Complications include occlusion of renal, iliac and/or mesenteric arteries with thrombus, emboli or rupture
Imaging: Double-barrel lumen of aorta

### Treatment
Surgical repair in asymptomatic patients with rapidly growing aneurysm of >5.0 cm; Immediate surgical repair for ruptured aneurysm; blood pressure control with beta-blockers and ACE inhibitors; smoking cessation; lipid lowering drugs
**Dissecting Aneurysm**

- Usually occur in the thoracic aorta
- Dissection along the media causes vascular occlusion and haemopericardium
Berry Aneurysm

- Occur in the circle of Willis
- Rupture causes subarachnoid haemorrhage
Bottom view of brain and major arteries of the brain

Berry aneurysm on the anterior communicating artery of the brain

Circle of Willis
Cerebral aneurysm

Blood vessels (arteries) in brain
Capillary Micro-Aneurysm

- May be intracerebral (in hypertension), causing cerebral haemorrhage

OR

- Retinal (in diabetes), causing diabetic retinopathy.
Syphilitic Aneurysm

- Usually occur in thoracic aorta

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

- Involvement of the vasa vasorum of the aorta is particularly devastating

- It results in ischemic medial injury, leading to aneurysmal dilatation of the aorta and aortic annulus and eventually valvular insufficiency
Mycotic (Infective) Aneurysm

- Atherosclerotic lesions infected by lodging of circulating microorganisms in the wall, particularly in the setting of bacterimia from a primary Salmonella gastroenteritis.

- Suppuration further destroys the media, potentiating rapid dilatation and rupture.

- Mycotic aneurysms can originate:
  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
Clinical Effects of Abdominal Aneurysm

- **Rupture** into abdominal cavity or retroperitoneal tissues with massive, potentially fatal haemorrhage

- **Obstruction** of a branch vessel resulting in downstream tissue ischemic injury - for example:
  - Ileic (Leg)
  - Renal (Kidney)
  - Mesenteric (Gastrointestinal tract)
  - Vertebral (Spinal cord) arteries

- **Embolism** from atheroma or mural thrombus
  Impingement on an adjacent structure, for example:
  - Compression of ureter
  - Erosion of vertebra

- **Presentation as an abdominal mass** (often palpably pulsating) that simulates a tumour
Clinical Features of Thoracic Aneurysm

- Encroachment on mediastinal structures
- Respiratory difficulties caused by encroachment on the lungs and airways
- Difficulty in swallowing caused by compression of the esophagus
- Persistent cough from irritation of the recurrent laryngeal nerves
- Pain caused by erosion of bone (i.e., ribs and vertebral bodies)
- Cardiac disease due to valvular insufficiency or narrowing of the coronary ostia
- Aortic rupture
Diseases of Blood Vessels

AORTIC DISSECTIONS
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.
- Creates massive haemorrhage or cardiac tamponade (haemorrhage into the pericardial sac).
- Aortic dissection occurs principally in two epidemiologic groups:
  1. Men aged 40 to 60 years, with antecedent hypertension (more than 90% of cases of dissection).
  2. Younger patients with systemic or localized abnormalities of connective tissue affecting the aorta (e.g., Marfan Syndrome).
**Aortic Dissection-Pathogenesis**

- **HYPERTENSION** is the major risk factor for aortic dissection. Aortas in hypertensive patients show medial hypertrophy of the vasa vasorum associated with extracellular matrix degenerative changes and variable loss of medial smooth muscle cells, suggesting that pressure-related mechanical injury and/or ischemic injury (due to diminished flow through the vasa vasorum) is somehow contributory.

- A considerable smaller number of dissections is related to inherited or acquired connective tissue disorders causing abnormal vascular connective tissue disorders causing abnormal vascular extracellular matrix:
  - Marfan Syndrome
  - Ehlers-Danlos Syndrome
  - Vitamin – C Deficiency
  - Copper Metabolic Defects
Aortic Dissection - Morphology

- In the vast majority of the spontaneous dissections, 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

- Sharp and 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 haematomas 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 haemorrhage
Double-Barreled Aorta:

- In some (lucky) 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-barrelled aorta” with a false channel).

- This averts a fatal extra-aortic haemorrhage.
**Aortic Dissection**

**A:** Gross photograph of an opened aorta with proximal dissection originating from a small, oblique intimal tear (identified by the probe), allowing blood to enter the media and create an intramural haematoma (narrow arrows). Not the intimal tear has occurred in a region largely free of atherosclerotic plaque and that the propagation of the intramural haematoma is arrested at a site more distally where atherosclerosis begins (broad arrow).

**B:** Histologic view of the dissection demonstrating an aortic intramural hematoma (asterisk). Aortic elastic layers are black and blood is red in this section, stained with the Movet stain.
Cystic Medial Degeneration

- The most frequent pre-existing histologically detectable lesion is cystic medial degeneration.

- It is characterized by elastic tissue fragmentation and separation of the elastic and smooth muscle cells elements of the media by cystic spaces filled with amorphous proteoglycan-rich extracellular matrix.

- Ultimately there may be large scale loss of elastic lamina.
Aortic Dissection- Cystic Medial Degeneration

Elastin is stained black

A: Cross-section of aortic media from a patient with Marfan syndrome, showing marked elastin fragmentation and formation of areas devoid of elastin that resembles cystic spaces (Astericks)

B: Normal media for comparison, showing the regular layered pattern of elastic tissue
Aortic Dissection - Clinical Course

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

- The most serious complications occur with dissections that involve the aorta from the valve to the arch.

- Aortic dissections are generally classified into two types (DeBakey Type I and II).
Aortic Dissection - Types

**DeBakey Type A**
- More common and dangerous
- Requires surgical intervention
- Type A is of two types:
  - **Type I:** Involves the ascending aorta
  - **Type II:** Involves both the ascending and descending aorta

**DeBakey Type B:**
- **Type III:** Dissections arise after the take off of the greater vessels
Aortic Dissection - Clinical Features

- Usually the patient is a 40 to 60 years old man with hypertension.

- Classic clinical symptoms of aortic dissection are the sudden onset of excruciating chest pain radiating to the back mimicking the pain of acute 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).

- 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 coronary, renal, mesenteric, or iliac arteries, causing critical vascular obstruction.
### Summary: Aneurysms and Dissection

<table>
<thead>
<tr>
<th>Aneurysms and Dissections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysms are congenital or acquired dilatations of the heart or blood vessels that involve the entire wall thickness. Complications are related to rupture, thrombosis and embolization.</td>
</tr>
<tr>
<td>Dissections occur when blood enters the wall of a vessel and separates the various layers. Complications arises as a result of rupture or obstruction of vessels branching off the aorta.</td>
</tr>
<tr>
<td>Aneurysms and dissections result from structural weakness of the vessel wall caused by loss of smooth muscle cells or insufficient extracellular matrix which can be a consequence of ischemia, genetic defects or defective matrix remodeling.</td>
</tr>
</tbody>
</table>
Diseases of Blood Vessels

VASCULITIS
**Vasculitis**

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

- Depending upon the vascular bed involved, the manifestations can be protean.

- Besides the findings referable to the specific tissue(s) involved, clinical manifestations common to these entities typically include constitutional signs and symptoms such as fever, myalgia, arthralgias and malaise.

- Vessels of any type in virtually any organ can be affected.

- Although several forms of vasculitis have a predilection for relatively large vessels, most affect small vessels (arterioles, capillaries and venules).
Vasculitis

Definition:
- Inflammation of Vessel Wall
- Vessel of any type, in any organ may be affected
- Around 20 primary forms of vasculitis are recognized

Outstanding Features:
- Vessel size
- Immune complexes
- Presence of specific autoantibodies
- Granuloma formation
- Organ tropism
- Population demographics
Some 20 primary forms of vasculitis are recognized.

Probably, infections can also indirectly induce a noninfectious vasculitis, for example by generating immune complexes or triggering cross-reactivity.
Noninfectious OR Immune Vasculitis

Chiefly arterial
Infectious (5%) vs. Non-infectious (95%)

NON-infectious are generally “AUTO”-IMMUNE

Persistent findings:
   Immune complexes
   Anti DNA Antibodies
   ANTI-NEUTROPHIL AB’s (Wegener’s, “Temporal”)
   ANTI-ENDOTHELIAL CELL AB’s (Kawasaki)

Often DRUG related (Hypersensitivity, e.g. Penicillin)
Noninfectious OR Immune Vasculitis

- Mechanisms Underlying Immune Vasculitis
- Types of Immune Vasculitis
Mechanisms Underlying Noninfectious OR Immune Vasculitis

1) Immune Complex Deposition

2) Anti-neutrophil Cytoplasmic Antibodies (ANCAs)

3) Anti-endothelial Cell Antibodies

4) Auto-reactive T- cells
1. **Immune Complex – Associated Vasculitis**

- Seen in immunologic disorders like SLE
- Antibody and complement are typically detected in lesions
- Circulating immune (antigen-antibody) complexes may also be seen – for example, DNA-anti-DNA complexes in SLE associated vasculitis

- Antibodies formed secondary to viral infections, for example, 30% patients of polyarteritis nodosa have an underlying Hepatitis- B infection with vasculitis attributable to complexes of hepatitis B surface antigen (HbsAg) and antibodies to HBsAg.

- Immune complex deposition is implicated in:
  (i) Drug hypersensitivity vasculitis
  (ii) vasculitis secondary to infections
2. Antineutrophil Cytoplasmic Antibodies

- Many patients with vasculitis have circulating antibodies that react with neutrophil cytoplasmic antigens, so called Anti Neutrophil Cytoplasmic Antibodies (ANCAs).

- ANCA –activated neutrophils degranulate and also cause injury by the release of reactive oxygen species.
## 2. Antineutrophil Cytoplasmic Antibodies – Types:

Two types

<table>
<thead>
<tr>
<th>Antiproteinase 3 (PR3-ANCA)</th>
<th>Anti-myeloperoxidase (MPO-ANCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously called <strong>c-ANCA</strong></td>
<td>Previously called <strong>p-ANCA</strong></td>
</tr>
<tr>
<td>Associated with:</td>
<td></td>
</tr>
<tr>
<td>(i) Wagner’s granulomatosis</td>
<td>Associate d with:</td>
</tr>
<tr>
<td></td>
<td>(i) Microscopic Polyangitis</td>
</tr>
<tr>
<td></td>
<td>and</td>
</tr>
<tr>
<td></td>
<td>(ii) Churg- Strauss Syndrome</td>
</tr>
</tbody>
</table>
Antineutrophil Cytoplasmic Antibodies (ANCA) can directly activate neutrophils, stimulating release of reactive oxygen species and proteolytic enzymes; in vascular bed they may lead to endothelial cell injury.
TNF-alpha and other cytokines

Activation of neutrophils and endothelial cells

Migration of PR3 and MPO antigens to the cell membrane and binding to circulating ANCA

Conformational change in neutrophil adhesion molecules

Adhesion of neutrophils to endothelium (no rolling)

Release of ROS from primed neutrophils

Endothelial damage

Secretion of inflammatory cytokines by activated neutrophils

Influx of inflammatory cells
This muscular artery demonstrates vasculitis with chronic inflammatory cell infiltrates. The endothelial cells have proliferated and the lumen is absent.

Often, vasculitis is a feature of an autoimmune disease, such as systemic lupus erythematosus as was present in this patient.

Vasculitis is uncommon and the various forms are confusing and difficult to diagnosis and classify.

Tests such as ANA and ANCA help.
3. **Anti-Endothelial Cell Antibodies**

- Antibodies to endothelial cells may predispose to certain vasculitides, for example Kawasaki disease.
Types of Noninfectious OR Immune Vasculitis

Large Vessel Vasculitis (aorta and large branches to extremities, Head and Neck)
- Giant – Cell (Temporal) Arteritis
- Takayasu Arteritis

Medium – Vessel Vasculitis (Main Visceral Arteries and their branches)
- Polyartiritis Nodosa
- Kawasaki Disease

Small Vessel Vasculitis (Arterioles, Venules, Capillaries and occasionally small arteries)
- Microscopic Polyangitis
- Wagener Granulomatosis
- Thromboangitis Obliterans (Burger Disease)
Diagrammatic Representation of the preferred sites of the vasculature involved by the major forms of vasculitis; The width of the trapezoids indicate the frequencies of involvement of various portions. Note the large-, medium-, and small-vessel vasculitis affects arteries, but only small-vessel vasculitis involves smaller than arteries. LCA: Leucocytoclastic Angitis
Vascular sites involved in the more common vasculitides and their presumptive etiology. Note the considerable overlap in distribution.
CARDIOVASCULAR SYSTEM

- Aorta
  - Large to medium-sized artery
    - Small artery
      - Arteriole
      - Capillary
  - Venule
  - Vein

- Cutaneous leukocytoclastic angiitis
- Henoch-Schönlein purpura and essential cryoglobulinemic vasculitis
- Microscopic polyangiitis (microscopic polyarteritis)
- Wegener's granulomatosis and Churg-Strauss syndrome
- Polyarteritis nodosa and Kawasaki disease
- Giant cell (temporal) arteritis and Takayasu's arteritis
TYPES OF VASCULITIDES
<table>
<thead>
<tr>
<th>Types of Arteritis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Giant cell arteritis</strong></td>
<td>temporal artery, &gt;50yrs, T cell mediated? Medial granulomatous → elastic lamina fragmentation. T cells + giant cells + macrophages. Medial scarring.</td>
</tr>
<tr>
<td><strong>Takayasu arteritis</strong></td>
<td>granulomatous, younger (&lt;50yrs), aortic arch, great BV, transmural fibrous thickening of aorta → narrow lumen. ocular disturbances, Pulseless disease. Histology same as above</td>
</tr>
<tr>
<td><strong>Kawasaki Disease</strong></td>
<td>Arteritis with mucocutaneous lymph node syndrome. infants &amp; children. coronary art++ → aneurysm &amp;/or thrombosis. Inflammation ++ entire thickness, Fibrinoid necrosis. T cell mediated.</td>
</tr>
</tbody>
</table>
### Types of Arteritis

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener Granulomatosis</td>
<td>Acute necrotizing granulomas respiratory tract, necrotizing/granulomatous vasculitis, focal necrotizing, crescentic glomerulonephritis. PR3-ANCA in 95%.</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>Allergic granulomatosis and angiitis. Eosinophil rich necrotizing vasculitis associated with asthma, allergic rhinitis, extravascular necrotizing granulomas &amp; eosinophilia. MPO-ANCA</td>
</tr>
</tbody>
</table>
Giant – Cell (Temporal ) Arteritis

- Giant-cell temporal arteritis is the most common of the vasculitides.

- It is a chronic, typically granulomatous inflammation of large to small-sized arteries.

- It principally affects the arteries in the head—especially the temporal

- Can also effect the vertebral and ophthalmic arteries, as well as aorta (Giant-Cell Arteritis)

- Pathogenesis: A T-cell mediated immune response to an unknown, possibly vessel wall antigen
Giant – Cell (Temporal) Arteritis - Morphology

- Nodular intimal thickening with reduction of the lumen and occasional thrombosis
- Classical lesions show granulomatous inflammation
- Infiltrate of lymphocytes, macrophages with multinucleated giant cells and fragmentation of internal elastic lamina
**Temporal (Giant Cell) Arteritis**

**A:** Temporal artery showing giant cells at the degenerating internal elastic membrane (arrow)

**B:** Elastic tissue stain demonstrating focal destruction of internal elastic membrane (arrow) and intimal thickening characteristic of long standing or healed arteritis

**C:** Temporal artery of a patient with temporal arteritis showing a thickened nodule and tender segment of a vessel on the surface of head (arrow)
Temporal arteritis is one manifestation of giant cell arteritis, which can affect mainly branches of external carotid artery, but sometimes also the great vessels at the aortic arch and coronaries. There is focal granulomatous inflammation of the media.
Giant cell (temporal) arteritis is uncommon before age 50. Patients may have a firm, palpable, painful temporal artery. The sedimentation rate is often markedly elevated (100 mm/hr or more). Half of patients have polymyalgia rheumatica.
Giant – Cell (Temporal ) Arteritis- Pathogenesis

- A T-Cell immune response to an as yet un-characterized vessel wall antigen

- Extraordinary predilection for temporal artery is unexplained, although one hypothesis is that vessels in various parts of body develop from anlagen (in embryology a part or organ in its earliest stage of development) and may therefore express unique antigens
Giant - Cell (Temporal) Arteritis: Clinical Features

- Symptoms may be vague and constitutional:
  - Fever
  - Fatigue
  - Weight loss
  - Facial pain
  - Headache

- Temporal artery may be painful to palpation

- Ocular symptoms: Range from diplopia to complete loss of vision

Ophthalmic artery involvement can lead to sudden and permanent blindness. Affected persons must be diagnosed and treated promptly.
Giant – Cell (Temporal ) Arteritis- Clinical Features

- Symptoms may be vague and constitutional:
  - Fever
  - Fatigue
  - Weight loss
  - Facial pain
  - Headache

- Temporal artery may be painful to palpation

- Occular symptoms: Range from diplopia to complete loss of vision
# Giant–Cell (Temporal) Arteritis - Summary

<table>
<thead>
<tr>
<th><strong>Giant-Cell Arteritis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology and Epidemiology</strong></td>
</tr>
<tr>
<td>Etiology unknown, although T-cell mediated injury has been suggested; Usually affects people aged &gt;50 years and is more commonly seen in women</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
</tr>
<tr>
<td>Gross: Affects small and medium-sized arteries, usually branches of carotid artery (especially temporal)</td>
</tr>
<tr>
<td>Microscopic: Granulomatous inflammation of media with mononuclear infiltrate; giant cells</td>
</tr>
<tr>
<td><strong>Clinical Manifestations</strong></td>
</tr>
<tr>
<td>Unilateral throbbing headache; tender nodules along temporal artery course; jaw claudication (pain when chewing); impaired vision (caused by occlusion of ophthalmic artery); 50% of patients have systemic polymyalgia rheumatica (pain and stiffness of proximal muscles i.e., shoulder and pelvic muscles, most commonly in the morning)</td>
</tr>
<tr>
<td>Lab Findings: Markedly elevated ESR</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>
Takayasu Arteritis

- Granulomatous vasculitis of medium and larger arteries

- Characterized by ocular disturbances and marked weakening of the pulses in the upper extremities (hence its name “Pulse Less Disease”)

- Manifests with transmural fibrous thickening of the aorta particularly the aortic arch and great vessels

- Leading to severe narrowing of the major branch vessels

- Traditionally associated with Japanese people

- Occurs most frequently in women younger than 40 years

- Immune mechanisms are suspected
Takayasu Arteritis

- Aortic lesions of Takayasu Arteritis shows many similarities with Giant Cell Arteritis

- Distinction is then made on the basis of age

- Patients more than 50 years of age - Giant Cell Arteritis
  AND
  Patients less than 50 years of age - Takayasu Arteritis
Takayasu Arteritis - Morphology

- Classically involves aortic arch

- Gross changes include intimal hyperplasia and irregular thickening of the vessel wall

- Origin for the great vessels can be obliterated. Such narrowing explains the weakness of the peripheral pulses

- Histologically the changes range from adventitial mononuclear infiltrates to granulomatous inflammations
Takayasu Arteritis

A: Aortic arch angiogram showing narrowing of the vessels (arrows)

B: Gross photograph of two cross sections of right carotid artery demonstrating marked intimal thickening and minimal residual lumen

C: Histological view, illustrating destruction and fibrosis of the arterial media and an infiltrate of mononuclear inflammation, including giant cells
Takayasu Arteritis- Clinical Features

- **Initial symptoms:** Non-specific, including fever, weight loss, fatigue

- **With progression vascular symptoms appear**

- **Vascular symptoms:**
  - Hypotension
  - Weaker pulses in the upper extremities relative to the lower extremities
  - Coldness and numbness of fingers
# Takayasu Arteritis - Summary

<table>
<thead>
<tr>
<th>Etiology and Epidemiology</th>
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</thead>
<tbody>
<tr>
<td>Etiology unknown, although immune mechanisms are suspected; Most affects young women in their 30s and 50s</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross: Disease of medium and large arteries resulting in thickening of aortic arch or proximal great vessels and thus vascular insufficiency</td>
</tr>
<tr>
<td>Microscopic: Mononuclear infiltrate with perivascular cuffing of vasa vasorum in adventia and media and granulomatous changes with giant cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever; weak pulses in upper extremity (&quot;pulse-less disease&quot;); arthralgias; syncope; skin nodules; night sweats; claudication (bruits may be heard over the subclavian arteries); visual and neurologic disturbances</td>
</tr>
<tr>
<td>Lab: Markedly elevated ESR</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids; cyclophosphamide or methotraxate may be needed in severe cases</td>
</tr>
</tbody>
</table>
Polyarteritis Nodosa

- Polyarteritis nodosa is a systemic vasculitis of small or medium-sized vessels (but not arterioles, capillaries, or venules).

- Typically involve renal and visceral vessels but sparing pulmonary circulation.

- A third of patients have Chronic Hepatitis B infection, which leads to the formation of immune complexes containing hepatitis B antigens that deposit in affected vessels.
Polyarteritis Nodosa - Morphology

- Classical Polyarteritis Nodosa is characterized by **segmental transmural necrotizing inflammation** of small to medium sized arteries.

- Vessels of the kidney, heart, liver and GI tract are involved in descending order of frequency.

- Lesions usually involve only part of vessels circumference. The inflammatory process weakens the blood vessel wall and can lead to aneurysm or can rupture.

- During 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.

- Later the acute inflammatory infiltrate is replaced by fibrous (occasionally nodular) thickening of the vessel wall.

- Characteristically all the events can coexist. Signifying an ongoing process.
This is a segmental fibrinoid necrosis and thrombotic occlusion of the lumen of this artery. Note that part of the vessel wall at the upper right (arrow) is uninvolved.
Fibrinioid Necrosis in an artery in a patient with polyarteritis nodosa. The wall of the artery shows a circumferential bright pink area of necrosis with protein deposition and inflammation (dark nuclei of neutrophils (arrow) is uninvolved.
Fibrinoid Necrosis and heavy cell infiltration in a medium sized artery in a patient with polyarteritis nodosa
Polyarteritis Nodosa

[Diagram showing the pathology of Polyarteritis Nodosa, with labels for Complex-Mediated Inflammation, Complement, Neutrophil, Platelet aggregation, Fibrinoid necrosis, Neutrophil lysosomal enzymes.]
Polyarteritis Nodosa - Clinical Course

- Primarily disease of young adults / can affect other ages as well
- Course may be
  - Acute
  - Chronic
  - Episodic
- Symptoms (apart from general symptoms) depend upon the site of involvement e.g.
  - Hypertension
  - GI lesions
  - GN
- Biopsy confirms the diagnosis
- There is association with ANCA
- Association with HBV (30%) found
### Polyarteritis Nodosa

#### Etiology and Epidemiology

Etiology unknown but associated with Hepatitis B infection in 30% to 50% of patients; primarily affects middle-aged men but can occur in any age group of both sexes.

#### Pathology

**Gross:** Affect small-or medium–sized muscular arteries, especially at branch points of vessels of the kidney, heart, liver or gastrointestinal tract; lesions are of different ages.

**Microscopic:** Transmural inflammation of arterial wall with neutrophil, eosinophils and mononuclear infiltrate; fibrinoid necrosis may be present.

#### Clinical Manifestations

Fever; Weight loss; malaise; abdominal pain with associated nausea and vomiting; arthralgia; renal failure; peripheral neuropathy; hypertension; cotton–wool spots (retinal occlusion); myocarditis; pericarditis; palpable purpura.

Lab Findings: Elevated ESR; Leukocytosis.

#### Treatment

Carticosteroids; azathioprine; cyclophosphamids; antiviral therapy for HBV-related disease.
KAWASAKI DISEASE

- Is an Acute febrile usually self limiting illness of Childhood
- 80% CHILDREN <4
- Originally described in Japan
- Fatal in only 1%
- Affects large- medium, sometimes small arteries
- Its clinical significance stem from the involvement of coronary arteries
- Coronary arteritis can cause aneurysms that rupture or thrombose, resulting in myocardial infarction
- LEADING cause of ACQUIRED heart disease in children
Kawasaki Disease- Etiology

- Uncertain…. Probably delayed hypersensitivity response of T cells...
- Cytokine production & B cell activation……. Formation of Auto antibodies to ECs and SMCs
- A variety of infectious agents (most likely viral infection) trigger the disease

Clinical course

Typically manifests with conjunctival and oral erythema and blistering, edema of the hands and feet, erythema of palms and soles
Desquamated rash and cervical lymphadenopathy
Approximately 20% of untreated patients develop cardiovascular sequelae
Kawasaki Disease - Morphology

Profound inflammatory response involving entire thickness of vessel wall

Fibrinoid necrosis ....less prominent

Healed lesions/fibrosis/obstructive lesions
Kawasaki Syndrome

- High persistent fever
- Enlarged lymph nodes & swelling of the neck
- Sore throat
- Joint pain
- Swollen hands & feet, peeling skin on hands, palms, toes, soles of feet
- Redness of the eyes
- Red, chapped, cracked lips
- Patchy skin rash
- Coronary artery aneurysms
- Heart muscle inflammation
- Diarrhea
# Kawasaki Disease-Summary

<table>
<thead>
<tr>
<th><strong>Kawasaki Disease</strong></th>
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<tbody>
<tr>
<td><strong>Etiology and Epidemiology</strong></td>
</tr>
<tr>
<td>Etiology unknown, although defect in immune system regulation is suspected; Usually affects infants and young children aged &lt;5 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pathology</strong></th>
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</thead>
<tbody>
<tr>
<td>Gross: Affects small-and medium-sized vessels including coronary</td>
</tr>
<tr>
<td>Microscopic: transmural inflammation and necrosis of vessel wall with inflammatory infiltrate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Clinical Manifestations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever; congested conjunctiva; mucocutaneous lesions (oral mucosa); cervical lymphadenitis (usually one neck node); arthralgias; edema of hands and feet; erythema of palms and soles of feet</td>
</tr>
<tr>
<td>Complications include myocarditis, coronary artery aneurysms, which can rupture and lead to death</td>
</tr>
</tbody>
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<thead>
<tr>
<th><strong>Treatment</strong></th>
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</thead>
<tbody>
<tr>
<td>Aspirin; IV gamma-globulins (prevents coronary aneurysm); Disease is usually self-limited although patients should receive an echocardiogram or cardiac CT to evaluate for proximal coronary aneurysms</td>
</tr>
</tbody>
</table>
Wegener Granulomatosis

M>F, often in 40’s

Triad of findings:
1. Granulomas of the lung and/or upper respiratory tract (ear, nose, sinuses, throat)
2. Vasculitis of small to medium-sized vessels (capillaries, venules, arterioles and arteries), most prominently in the lungs and upper respiratory tract
3. Glomerulonephritis

ANTI-NEUTROPHIL-CYTOPLASMIC-AB’s (ANCA) usually present (95%)
Wegener Granulomatosis

- Limited disease remain confined to respiratory tract
- Widespread disease can involve eyes, skin and other organs, notably heart
- Is likely to be initiated as a cell mediated hypersensitivity response directed against inhaled infectious or environmental antigens
- PR3-ANCA are present in almost 95% of cases and probably drive the subsequent tissue injury
Wegener Granulomatosis-Morphology

- Upper respiratory lesions range from granulomatous sinusitis to ulcerative lesions of the nose, palate or pharynx

- There is multifocal necrotizing granulomatous vasculitis with a surrounding fibroblastic proliferation

- Multiple granulomas join to produce radiographically visible central cavitation

- **Renal lesions**: Focal and segmental necrotizing glomerulonephritis to more advanced glomerular lesions with diffuse necrosis and parietal cell proliferation forming epithelial crescents (Crescentic Glomerulonephritis)
Wegener Granulomatosis-Morphology
Wagner’s Granulomatosis-Lung Findings

Ulceration
Necrosis
granulomas
Fibrosis
organization
Wagner’s Granulomatosis—Clinical Features

- Typical patient is a 40-years old man
- Classic presentation includes bilateral pneumonitis with nodules and cavitary lesions, chronic sinusitis, mucosal ulceration of nasopharynx and renal disease.
- If untreated mortality is 80% at 1 year of disease
Wegener's Granulomatosis

Wegener's is infamous for its subtle presentation, and its lethality if it is not correctly diagnosed and treated.

It is caused by autoantibodies against proteinase 3.

- Sore Eye
- Sore Ear
- Stuffy Nose

- Destruction of the Face
- Lung Cavities & Bleeding
- Permanent Kidney Damage & Failure
- Gangrene

Positive c-ANCA (Anti-neutrophil cytoplasm Test)

Granulomas & patchy necrosis in arteries & veins

*Trace of blood in urine
# Wegener Granulomatosis - Summary

<table>
<thead>
<tr>
<th><strong>Wegener granulomatosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology and Epidemiology</strong></td>
</tr>
<tr>
<td>Caused by an immunologic mechanism (perhaps hypersensitivity reaction); Tends to affect men aged 40-60 years but can occur at any age</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pathology</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross: Vascular granulomatous lesions in the upper respiratory tract, lungs and kidneys</td>
</tr>
<tr>
<td>Microscopic: Necrotizing granulomas with necrotic centre surrounded by lymphocytes, macrophages and giant cell in vascular walls; granulomatous vasculitis with inflammatory infiltrate surrounded by fibroplastic proliferation; rapidly progressive glomerulonephritis seen in renal biopsy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Clinical Manifestations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforation of nasal septum; chronic sinusitis; otitis media; dyspnea; hemoptysis; hematuria; rash; myalgias; increased risk of DVTs</td>
</tr>
<tr>
<td>Complications include renal failure (nephrotic syndrome) and deafness</td>
</tr>
<tr>
<td>Lab Findings: c-ANCA positive; RBCs and/or RBC casts in urine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide and/or Prednisolone for initial therapy; methotrexate as maintenance therapy</td>
</tr>
</tbody>
</table>
## Wegener Granulomatosis vs Churg-Strauss Vasculitis

<table>
<thead>
<tr>
<th>Wegener's Granulomatosis</th>
<th>Churg Strauss Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-ANCA Positive</td>
<td>p-ANCA Positive</td>
</tr>
</tbody>
</table>
Churg-Strauss Vasculitis

- **Churg – Strauss syndrome** (also called allergic granuloma tosis and angitis) is a small vessel necrotizing vasculitis classically associated with asthma, allergic rhinitis, lung infiltrates, peripheral blood eosinophilia, extravascular necrotizing granulomas and a striking infiltration of vessels and perivascular tissue by eosinophilia.

- Cutaneous involvement (with palpable purpura), gastrointestinal bleeding, and renal disease (primarily as focal and segmental glomerulonephritis) are the major associations.

- Cytotoxicity produced by the myocardial eosinophilic infiltrate often leads to cardiomyopathy; cardiac involvement seen in 60%.

- **Churg-Strauss syndrome** may stem from “hyperresponsiveness” to some normally innocuous allergic stimulus.

- The vascular lesions differ from those of polyarteritis nodosa or microscopic polyangitis by virtue of presence of granulomas and eosinophils.
# Churg-Strauss Vasculitis -Summary

<table>
<thead>
<tr>
<th>Churg-Strauss Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology and Epidemiology</strong></td>
</tr>
<tr>
<td>Etiology is unknown, but some form of autoimmunity is thought to contribute to the disease</td>
</tr>
<tr>
<td>Primarily affects middle–aged men but can occur in any age group of both sexes</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
</tr>
<tr>
<td>Gross: Affects small-to medium-sized muscular arteries and veins, especially in vessels of the lung, kidney, heart, spleen, skin to gastrointestinal tract</td>
</tr>
<tr>
<td>Microscopic: Inflammation of arterial wall with predilection of lymphocytic (and eosinophilic) infiltrate in adventitia; fibrinoid necrosis may be present</td>
</tr>
<tr>
<td><strong>Clinical Manifestations</strong></td>
</tr>
<tr>
<td>Classically presents with late–onset asthma, sinusitis and rhinitis, pulmonary involvement with pulmonary infiltrates presenting as cough and polyneuropathy (specifically mononeuritis multiplex).</td>
</tr>
<tr>
<td>Lab findings: Elevated ESR; Eosinophilia, 40% of patients will be p-ANCa positive</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>High-dose corticosteroids; cyclophosphamide</td>
</tr>
</tbody>
</table>
THROMBOANGIITIS OBLITERANS-BUERGER(‘s) Disease

- 100% caused by cigarette smoking
- MEN>>>F, 30’s, 40’s
- Often arteries are 100% obliterated, hence the name “obliterans”
- EXTREMITIES most often involved (tibial and radial arteries
- Etiology is unknown; Direct endothelial cell toxicity by some component of tobacco is suspected; alternatively a reactive compound in tobacco may modify vessel wall components and induce an immune response
- Morphology: Sharply segmental acute and chronic transmural vasculitis of medium and small arteries
Thromboangitis Obliterans (Burger Disease) - Clinical Presentation

- **Superficial nodular phlebitis**
- Cold induced Reynaud's phenomenon, instep foot pain induced by exercise (instep claudication)
- Chronic ulceration of toes, feet, fingers,
- Severe pain even at rest
- Chronic extremity ulcerations can develop, progressing over time (occasionally precipitously) to frank gangrene
Characterized by:
Sharply segmental acute and chronic vasculitis of medium sized and small arteries predominantly of extremities
Luminal thrombosis
Micro-abscesses
Granulomatous inflammation
Thromboangiitis Obliterans (Buerger’s disease)

- Limited Vasculitis
- Sites = Tibial & Radial arteries
- Age = <35yrs., M>F, Smokers, Asians
- Clinical = intermittent claudication, rest pain (neural involvement), ulcerations of Toes, Fingers
- Pathology / Morphology = Granulomatous inflammation, Thrombi with central micro abscess (Pus)
- Diagnosis = Biopsy,
- Treatment = Avoidance of smoking, Surgery, Prostaglandin analogues
- Complications = ulcers, gangrene, infection need of amputation
Localized arteritis may be caused by the direct invasion of arteries by infectious agents, usually bacteria or fungi and in particular Aspergillus and Mucor spp.

Vascular invasion can be part of a more general tissue infection or less commonly arise from hematogenous spread of bacteria.

Vascular infections can weaken arterial walls and culminate in Mycotic Aneurysms or can induce thrombosis and infarction.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Features</th>
<th>Vessels involved</th>
<th>Antigenic stimulus</th>
<th>Auto-antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyarteritis Nodosa</td>
<td>Microinfarcts and haemorrhages from aneurysms</td>
<td>Muscular arteries</td>
<td>HbsAg in some cases</td>
<td>Non consistently</td>
</tr>
<tr>
<td>Rheumatoid Vasculitis</td>
<td>Arthritis Cutaneous vasculitis</td>
<td>Aorta, arteries and arterioles</td>
<td>DNA in some cells</td>
<td>Anti-DNA Rheumatoid factor</td>
</tr>
<tr>
<td>Wegner’s granulomatosis</td>
<td>Destructive nasal lesions Lung and renal lesions</td>
<td>Arteries, arterioles and venules</td>
<td>Not known</td>
<td>Ant-neutrophil cytoplasmic antibody (ANCA)</td>
</tr>
<tr>
<td>Systemic Lupus Erythromatosus</td>
<td>Skin rash Renal disease</td>
<td>Arterioles and capillaries</td>
<td>DNA and RNA in some cases</td>
<td>Anti-DNA</td>
</tr>
</tbody>
</table>
**Vasculitis Summary**

<table>
<thead>
<tr>
<th>Vasculitis - Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis is defined as inflammation of vessel walls; it frequently is associated with systemic manifestations (including fever, malaise, myalgias and arthralgias) and organ dysfunction that depends on the pattern of vascular involvement.</td>
</tr>
<tr>
<td>Vasculitis can result from infections but more commonly has an immunologic basis such as immune complex deposition, antineutrophil antibodies (ANCAs), or antiendothelial cell antibodies.</td>
</tr>
<tr>
<td>Different forms of vasculitis tend to specifically affect vessels of a particular caliber and location.</td>
</tr>
</tbody>
</table>
Raynaud Phenomenon

It results from exaggerated vasoconstriction of arteries and arterioles in the extremities, particularly the fingers and toes, but also sometimes the nose, earlobes or lips.

The restricted blood flow induces paroxysmal pallor or cyanosis involves digits

Characteristically show “Red-White-and-Blue” colour changes from most proximal to most digital, reflecting proximal vasodilation, central vasoconstriction and more distal cyanosis, respectively.

Two Types of Raynaud Phenomenon:

1. Primary Raynaud Phenomenon
2. Secondary Raynaud Phenomenon
Primary Raynaud Phenomenon

- Previously called Raynaud Disease
- Caused by exaggerated central and local vasomotor responses to cold or emotions
- Affects 3 to 5% of general population
- Has a predilection for young women
- Structural changes in blood vessels are absent, except in late stages when intimal thickening may appear
- Course is usually benign, but in chronic cases, atrophy of the skin, subcutaneous tissues and muscles may occur
Secondary Raynaud Phenomenon

Refer to vascular insufficiency due to arterial disease caused by other entities including:

- Systemic Lupus Erythematosus
- Scleroderma
- Burger disease
- Atherosclerosis

Raynaud Phenomenon may be the first manifestation of such conditions; So every patient with Raynaud Phenomenon should be evaluated for secondary causes
Diseases of Blood Vessels

TUMOURS
Tumours of Blood Vessels

- Include common and benign hemangiomas, locally aggressive neoplasms that metastasize infrequently, and rare, highly malignant angiosarcomas.

- Primary tumours of large vessels are extremely rare.

- Vascular tumours can arise from endothelium (haemangimas, lymphangiomas, angiosarcoma) or cells that support or surround blood vessels (glomerus tumour).
Tumours of Blood Vessels – General Rules of Thumb

- Although a benign haemangioma usually can be distinguished with ease from an anaplastic high-grade angiosarcoma, on occasion the distinction between benign and malignant can be difficult. General rules of thumb are as follows:

1. Benign tumours usually contain obvious vascular channels filled with blood cells or lymph that are lined by a monolayer of normal appearing endothelial cells.

2. Malignant tumours are more cellular, show cytologic atypia, are proliferative, and usually do not form well-organized vessels; confirmation of the endothelial derivation of such proliferations may require immunohistochemical detection of endothelial cell-specific markers, such as CD31 or von Willebrand factor.
Benign Vs Malignant Tumours

**Benign tumors**
- Usually produce vascular channels filled with blood and
- Without cellular atypia
- Lined by monolayer of normal endothelial cells

**Malignant tumors**
- Do not form well formed vessels
- Cytological atypia
- Are more solid
- High mitotic figures

Borderline
## Classification of Vascular Tumours and Tumor–like Conditions

### Benign Neoplasms, Developmental and Acquired Conditions

- **Hemangiomas**: (Capillary Hemangioma, Cavernous Hemangioma, Pyogenic Granuloma)
- **Lymphangioma**: (Simple(Capillary)Lymhpangioma, Cavernous Lymphangioma, Cavernous Lymphangioma(Cystic Hygroma)
- **Glomus Tumour**
- **Vascular Ectasias**: (Nevus Flammeus, Spider Telangiectasia (Arterial Spider), Heriditary Hemorrhagic Telangiectasis (Osler-Weber –Rendu Disease)
- **Reactive Vascular Proliferations**: Bacillary Angiomatosis

### Intermediate Grade Neoplasms

- **Kaposi Sarcoma**
- **Hemangioendothelioma**

### Malignant Neoplasms

- **Angiosarcoma**
<table>
<thead>
<tr>
<th>Benign tumours, Developmental and acquired conditions</th>
<th>Intermediate grade neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemangioma</strong>&lt;br&gt;Capillary hemangioma&lt;br&gt;Cavernous hemangioma&lt;br&gt;Pyogenic granuloma</td>
<td><strong>Kaposi sarcoma</strong>&lt;br&gt;<strong>Hemangioendothelioma</strong></td>
</tr>
<tr>
<td><strong>Lymphangioma</strong>&lt;br&gt;Simple (capillary) lymphangioma&lt;br&gt;Cavernous Lymphangioma (Cystic hygroma)</td>
<td></td>
</tr>
<tr>
<td><strong>Glomus tumour (Glomangioma)</strong></td>
<td><strong>Malignant neoplasms</strong></td>
</tr>
<tr>
<td><strong>Vascular ectasias</strong>&lt;br&gt;Naevus flammus&lt;br&gt;Spider telangiectasis&lt;br&gt;Hereditary hemorrhagic telangiectasias (Osler-Weber-Rendu Disease)</td>
<td><strong>Angiosarcoma</strong></td>
</tr>
<tr>
<td><strong>Reactive vascular proliferations</strong>&lt;br&gt;Bacillary angiomatosis</td>
<td></td>
</tr>
</tbody>
</table>
Ectasia is a generic term for any local dilatation of a structure, while Telangiectasias is used to describe a permanent dilation of preexisting small vessels (capillaries, venules, and arterioles, usually in the skin or mucous membranes) that form a discrete red lesion. These lesions can be congenital or acquired and are not true neoplasm.

Different Vascular Ectasias

- Nevus Flammeus
- Port Wine Stain
- Spider Telangiectasia
- Hereditary Hemorrhagic Telangiectasia
Nevus Flammeus

- Nevus flammeus (a ‘birth mark’), the most common form of vascular ectasia.

- Is a light pink to deep purple flat lesion on the head or neck composed of dilated vessels.

- Most ultimately regress spontaneously
VASCULAR ECTASIAS

**Port Wine Stain**

- It is a special form of nevus flammeus.
- These lesions tend to grow during childhood, thicken the skin surface, and do not fade with time.
- Such lesions occurring in the distribution of the trigeminal nerve are associated with the Sturge–Weber Syndrome.
VASCULAR ECTASIAS

**Spider Telangiectasias**

- Are non-neoplastic vascular lesions with a general shape resembling that of a spider.
- These lesions manifest as radial, often pulsatile arrays of dilated subcutaneous arteries or arterioles (the “legs” of the spider) about a central core (the spider’s body) that blanch with pressure.
- Spider telangiectasias commonly occur on the face, neck, or upper chest.
- Most frequently are associated with hyperestrogenic states (e.g., in pregnant women or patients with cirrhosis).
Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

- It is an autosomal dominant disorder caused by mutations in genes that encode components of TGF-β signaling pathway in endothelial cells.
- The telangiectasias are malformations composed of dilated capillaries and veins that are present at birth.
- These are widely distributed over the skin and oral mucous membranes, as well as in respiratory, gastrointestinal, and urinary tracts.
- These lesions can spontaneously rupture, causing serious epistaxis (nosebleed), gastrointestinal bleeding or hematuria.
Hemangiomas

- Are very common tumors
- Increased number of normal or abnormal vessels filled with blood
- 7% of all benign tumors of infancy and childhood
- May be seen in superficial lesions of body e.g. head or neck
- Can occur internally, 1/3rd being found in liver
- May involve the large portion of the body (angiomatosis)
- Various clinical and histological variants:
  1. Capillary Haemangioma
  2. Juvenile Haemangioma
  3. Pyogenic Haemangioma
  4. Cavernous Haemangioma
Haemangiomas
Capillary Haemangioma

- The most common variant
- Mainly occur in skin, s/c tissue and mucous membrane of oral cavity and lips
- Also seen in liver, spleen and kidneys
- Also called “juvenile”, and “Strawberry type”
- Usually regress with age

Gross

- Are bright red to blue
- A few mm to several cms
- Flat or elevated

M/S

- Unencapsulated aggregates of closely packed, thin walled capillaries
- Filled with blood
- Lined by endothelium
- Vessels may thrombose/organized
- Rupture...Hemosidrin deposition
- Focal Scarring
Histologically:
Lobulated
Unencapsulated
Closely packed thin walled capillaries
Flat endothelium
Scanty stroma
Thrombosed lumen
Hemosiderin & focal scarring
Capillary Haemangioma - Morphology

**Gross Appearance**
Red blue soft spongy masses 1-2 cm in diameter
Rare giant forms may be seen on subcutaneous areas of face, extremities and other body regions

**Microscopic features**
The mass is circumscribed, not encapsulated
Composed of large dilated vascular channels filled with blood separated by mild-moderate CT
Intravascular thrombosis
Dystrophic calcification
Traumatic ulceration
Bleeding
Strawberry hemangioma (1/200 live births) newborns

- Grows and regresses
Cavernous Hemangiomas

- Large dilated vascular spaces
- Also called “adult” Hemangiomas
- Less well circumscribed
- More frequently involve deeper structures
- Usually do NOT regress
- May be locally destructive
- Usually require surgery
PYOGENIC GRANULOMA

Most commonly in the oral cavity
Histology like capillary hemangioma
Regress
Indistinguishable from normal granulation tissue
LYMPHANGIOMA

benign lymphatic analogue of Hemangiomas

1. Simple capillary Lymphangiomas
   Small 1-2 mm
   90% Head and neck region in kids <2
   Generally......RARE

2. Cavernous Lymphangioma
   When large size and/or spaces present often called “CYSTIC HYGROMA”
   Seen in axillary region, neck or retroperitoneally
GLOMUS TUMOR (GLOMANGIOMA)

Arise from modified SMC of Glomus body
Glomus body is believed to function in thermal regulation
Average age at presentation- 30-50 yrs
1 cm
Most commonly under nail
Biologically benign but Painful
Most commonly found in distal region of digits especially under finger nails
Excision is curative
Gross
GT are round, slightly elevated red blue firm nodules (usually <1cm)
Glomus tumour: Microscopic picture

- Nests/masses of glomus cells with branching vascular channels within CT stroma
- Individual tumor cells are round or cuboidal with scant cytoplasm
Vascular neoplasm caused by KS herpes virus (KSHV- HHV-8)

Although it occurs in number of contexts, it is by far most common in patients with AIDS;

Indeed its presence is used as a criterion for the diagnosis of AIDS

Four subtypes:
(i) Classic KS
(ii) Endemic KS
(iii) Transplantation KS
(iv) HIV associated KS
Vascular neoplasm caused by KS herpes virus (KSHV- HHV-8)

**Classic KS:**
- HIV Negative; may be associated with malignancy or altered immunity
- Manifests as multiple, red-purple skin plaques or nodules, usually in distal, lower limbs.
- Lesions progressively increase in size and number, and spread proximally.
- Tumour usually remains localized

**Endemic African KS:**
- Younger age (<40 yrs)
- HIV Negative
- May follow indolent or aggressive course
- Involves LYMPH Nodes frequently

**HIV-associated KS:**
- KS is >1,000 times more common in AIDS than in general population
- It is the most common AIDS-associated malignancy
- It involves lymph nodes and can disseminate widely in early course of the disease

**Transplant associated KS:**
- Occurs in solid organ transplant recipients in the setting of T-cell immunosuppression.
Virtually all KS lesions are infected by KSHV. Like EB Virus, KSHV is a gamma-herpesvirus. It is transmitted both through sexual contact and by poorly understood nonsexual routes.

KSHV and altered T cell immunity probably are required for KS development.

A virally encoded G protein induces VEGF production, stimulating endothelial growth and cytokines produced by inflammatory cells recruited to sites of lytic infection also create a local proliferative milieu.

In latently infected cells, KSHV–encoded proteins disrupt normal cellular proliferation controls (e.g., through synthesis of a viral homologue of cyclin D) and prevent apoptosis by inhibiting p53.

Thus the local inflammatory environment favours cellular proliferation, and latently infected cells have a growth advantage.
Three stages can be identified: Patch; plaque; nodule

**PATCH:** Pink to red to purple solitary or multiple macules, initially confined to distal lower extremities or feet.

Microscopically, dilated, irregular and angulated blood vessels are seen. These are lined by normal looking ECs., with interspersed infiltrate of lymphocytes, plasma cells and macrophages

**Raised violaceous plaques:** The lesions spread proximally. They spread proximally, and into the dermis. They are dilated, and jagged, and are lined by plump spindle cells

**Nodules:** The lesions extend further, and are lined by plump spindle cells showing more marked atypia
Kaposi Sarcoma: Characteristic coalescent red-purple papules and plaque
A: Kaposi Sarcoma: Characteristic coalescent red-purple papules and plaque
B: Histologic view of the nodular stage demonstrating sheets of plump, proliferating spindle cells and slit-like vascular spaces
Vascular channels containing red blood cells are prominent.

Atypical cells with hyperchromatic nuclei.
fascicles of neoplastic endothelial cells

erythrocytes in small collection

fascicles of neoplastic endothelial cells
Diagnosis of vascular neoplasms may require the use of EC markers such as Factor VIII or CD-31, especially if clear cut vascular spaces are difficult to see, and if the tumor is UNDIFFERENTIATED and endothelial lined spaces are NOT clearly seen.
**Kaposi Sarcoma**

### Etiology and Pathogenesis

Etiology is unknown; however, viral origin and association with immune status are being investigated. Three variants:

1. **Classic KS**: seen in older men of Ashkenazi Jewish or Mediterranean descent; 
2. **(Endemic African) KS**: seen in young African men and children; 
3. **Epidemic KS**: caused by human herpes virus type 8; associated with AIDS, especially in homosexual men with low CD4 counts.

### Pathology

- **Gross**: Reddish macules that become raised plaques and nodules over time; begins in skin but can spread to lymph nodes and viscera (i.e., lungs and gastrointestinal tract).
- **Microscopic**: Dilated blood vessels with an endothelial mononuclear infiltrate; will progress to see spindle cells with hyaline globules, mitotic figures and hemosidrin pigment.

### Clinical Manifestations

- Painless, reddish-purpule, raised plaques and firm nonpurpuritic nodules; lymphadenopathy; hemoptysis; dyspnea; abdominal pain and gastrointestinal bleeding.
- Lab Findings: Specific KSHV antibodies present in 70-90% of time.

### Treatment

- Reduce HIV viral load and raise CD4 count with antiviral therapy; Treat limited disease with intralesional vinblastine or topical treatments. Treat systemic disease with chemotherapy.

### Notes

- Kaposi sarcome, Non Hodgkins Lymphoma, CNS Lymphomas and Cervical cancer are cancers commonly associated with AIDS.
Malignancies Associated with HIV

- Kaposi sarcome
- Non Hodgkins Lymphoma
- CNS Lymphomas
- Cervical cancer
HEMANGIOENDOTHELIOMA

Wide spectrum of borderline vascular neoplasia
Clinical behaviour is intermediate between benign and malignant trs.
Epithelioid hemangioendothelioma:
Adults
Arises in association with medium-sized to large veins.
Clinical course is highly variable
Excision is curative in majority
Upto 40% recur; 20-30% metastasize
Tumour cells are plump and cuboidal, and do not form well defined vascular channels
HEMANGIOPERICYTOMA

- HETEROGENOUS group of disorders
- Arise from pericytes- myofibroblast-like cells that surround capillaries and veins.
- Most commonly arising in pelvic retroperitoneum
MALIGNANT VASCULAR TUMORS

ANGIOSARCOMA
Malignant endothelial neoplasms
Well differentiated to wildly anaplastic lesions
Older adults are more commonly affected
Equal in males and females
May occur at any site; more common in skin, soft tissue, breast and liver
Hepatic Angiosarcoma has been associated with certain carcinogens:
arsenical pesticides; thoratrast; polyvinyl chloride (Plastic)
Skin: begin as small sharply demarcated red nodules.
Larger lesions are fleshy, red tan to grey white masses, with margins that blend with the surrounding imperceptibly.
Necrosis and hemorrhages are common.

Plump atypical Endothelial cells forming vascular channels to undifferentiated spindle cells without discernible blood vessels- May not look “vascular”
Frequent and often bizarre mitoses are present
CD31 and vWF positive
Behave as any sarcoma might, i.e., early pulmonary metastases
**Angiosarcoma**: Moderately differentiated angiosarcoma with dense clumps of atypical cells lining distinct vascular lumina.
ANGIOSARCOMA: Immunohistochemical staining of angiosarcoma for the endothelial cell marker CD31
**VASCULAR TUMORS - Summary**

<table>
<thead>
<tr>
<th>VASCULAR TUMORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular Ectasias</strong> are not neoplasms but rather dilations of existing vessels</td>
</tr>
<tr>
<td>Vascular tumours can be derived from either blood vessels or from lymphatics</td>
</tr>
<tr>
<td>Can be composed of <em>endothelial cells</em> (hemangiomas, lymphangiomamas, angiosarcomas) OR <em>other cells</em> of the vascular wall (e.g., glomus tumour)</td>
</tr>
<tr>
<td>Most vascular tumours are <strong>benign</strong> (e.g., hemangiomas); some have an intermediate, locally aggressive behaviour (e.g., Kaposi sarcoma); others are highly malignant (e.g., Angiosarcoma)</td>
</tr>
</tbody>
</table>
Diseases of The Heart
The heart is a vitally life sustaining organ.

It is responsible for pumping more than 6000 liters of blood daily through the body.

In its normal, healthy state it perfuses tissues with a steady state of supply of vital nutrients and facilitates the removal of waste products.
When pathology supervenes, cardiac dysfunction is associated with devastating physiologic consequences.

Heart disease remains the leading cause of morbidity and mortality in industrialized nations.
# Diseases of Heart - An Overview

## Heart Failure
- **Left Sided Heart Failure**
- **Right Sided Heart Failure**

## Pericardial Disease
- **Pericarditis**
- **Pericardial Effusions**

## Congenital Heart Disease
- **Left to Right Shunts** (Atrial Septal Defects; Ventricular Septal Defects; Patent Ductus Arteriosus)
- **Obstructive Lesions** (Aortic Coarctation)

## Ischemic Heart Disease
- **Angina Pectoris**
- **Myocardial Infarction**
- **Chronic Ischemic Heart Disease**
- **Sudden Cardiac Death**

## Hypertensive Heart Disease
- **The Pathophysiology of Cardiac Hypertrophy**
- **Systemic Hypertensive Heart Disease**
- **Pulmonary Hypertensive Heart Disease** (Cor Pulmonale)

## Valvular Heart Disease
- **Calcific Aortic Stenosis**
- **Myxomatous Mitral Valve**
- **Rheumatic Valvular Disease**
- **Infective Endocarditis**
- **Noninfected Vegetations** (Nonbacterial Thrombotic Endocarditis; Libman-Sacks Endocarditis)
- **Carotid Heart Disease**
- **Prosthetic Cardiac Valves**

## Cardiomyopathies
- **Dilated Cardiomyopathy** (Arrhythmogenic Right Ventricular Cardiomyopathy)
- **Hypertrophic Cardiomyopathy**
- **Restricted Cardiomyopathy**
- **Myocarditis**

## Cardiac Tumours
- **Metastatic Neoplasms**
- **Primary Neoplasms**
Diseases of Heart

HEART FAILURE
Heart Failure (Congestive Heart Failure)

- Heart Failure is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support a physiological circulation.

- The incidence of heart failure increases with advancing age.

- The prognosis of heart failure has improved over the past 10 years, but the mortality rate is still high with approximately 50% of patients died at 5 years.

- Coronary Heart Disease is the commonest cause of heart failure in western countries.
## Heart Failure – Causes

### MAIN CAUSES OF CARDIAC FAILURE

- **Ischemic Heart Disease (35-40%)**
- **Cardiomyopathy (30-34%)**
- **Hypertension (15-20%)**

### OTHER CAUSES OF CARDIAC FAILURE

- **Cardiomyopathy (Undilated):** Hypertrophic/Obstructive, Restrictive(Amylodenosis, Sarcoidosis)
- **Valvular Heart Disease:** Mitral, Aortic, Tricuspid
- **Congenital Heart Disease:** (ASD, VSD)
- **Alcohol and Drugs:** (Chemotherapy)
- **Hyperdynamic Circulation:** (Anaemia; Thyrotoxicosis; Haemochromatosis; Paget’s Disease)
- **Right Heart Failure:** RV Infarct; Pulmonary Hypertension; Pulmonary Embolism; or Cor Pulmonale (COPD)
- **Tricuspid Incompetence**
- **Arrhythmias:** (Atrial Fibrillation; Bradycardia (Complete heart block, the sick sinus syndrome))
- **Pericardial Disease:** (Constrictive Pericarditis; Pericardial Effusion)
In a mechanical sense, the failing heart in congestive heart failure can no longer pump blood delivered to it by the venous circulation.

Inadequate cardiac output – called **Forward Failure**

Forward failure is almost always accompanied by increased congestion of the venous circulation, **Backward Failure** because the failing ventricle is unable to eject the venous blood delivered to it.

Although the root problem in congestive cardiac failure is typically abnormal cardiac function, virtually every other organ is eventually affected by some combination of forward or backward failure.
Adaptation of Cardiovascular System to Reduced Contractility OR Increased Haemodynamic Burden

The cardiovascular system can adept to reduced myocardial contractility or increased haemodynamic burden by a few different ways. The most important are:

1) Activation of Neurohumoral System
2) Frank-Starling Mechanism
3) Myocardial Structured Changes, including augmented muscle mass (hypertrophy)
Activation of Neurohumoral Systems

- Activation of neurohumoral systems include:

  1. Release of neurotransmitter Norepinephrine by the sympathetic nervous system (increases heart rate and augments myocardial contractility and vascular resistance)

  2. Activation of the renin-angiotensin-aldosterone system

  3. Release of atrial natriuretic peptide (ANP). This is a polypeptide hormone secreted by the atria in the setting of atrial distension. It causes vasodilatation, natriuresis and diuresis that help alleviate volume or pressure overload states
Frank – Starling Mechanism

- As cardiac failure progresses, end-diastolic pressures increases, causing individual cardiac muscle fiber to stretch; This ultimately increases the volume of the cardiac chamber.

- In relation with Frank-Starling relationship, these lengthened fibers initially contract more forcibly, thereby increasing cardiac output.

- **Compensated Heart Failure:** If the dilated ventricle is able to maintain cardiac output at a level that meets the needs of the body, the patient is said to be in compensated heart failure.

- **Decompensated Heart Failure:** Increasing dilatation increases ventricular wall tension, which increases the oxygen requirements of an already compromised myocardium. With time, the failing myocardium is no longer able to propel sufficient blood to meet the needs of the body, even at rest. At this point, patients enter a phase termed decompensated heart failure.
Myocardial Structural Changes, Including Augmented Muscle Mass (Hypertrophy)

- As adult cardiac myocytes cannot proliferate, adaptation to a chronically increased workload involves hypertrophy of individual muscle cells.

- **Concentric Hypertrophy:**
  - Seen in pressure overload states (Hypertension, valvular stenosis)
  - Characterized by increased diameter of individual muscle fibers
  - Thickness of the ventricular wall increases without an increase in the size of chamber

- **Eccentric Hypertrophy:**
  - Seen in volume overload states (valvular regurgitation or abnormal shunts)
  - Characterized by an increase in heart size as well as an increase in wall thickness
  - The length of individual muscle fiber increases
Initially then adaptive mechanisms may be adequate to maintain cardiac output in the face of declining cardiac performance.

However, with sustained or worsening heart function, pathologic changes may eventually supervene, resulting in structural and functional disturbances.
HYPERTENSION

- Pressure overload

VALVULAR DISEASE

- Pressure and/or volume overload
  - ↑ Cardiac work
  - ↑ Wall stress
  - Cell stretch
  - Hypertrophy and/or dilation
    - Characterized by
      - ↑ heart size and mass
      - ↑ protein synthesis
      - induction of immediate-early genes
      - induction of fetal gene program
      - abnormal proteins
      - fibrosis
      - inadequate vasculature
  - Cardiac dysfunction
    - Characterized by
      - heart failure (systolic/diastolic)
      - arrhythmias
      - neurohumoral stimulation

MYOCARDIAL INFARCTION

- Regional dysfunction with volume overload
Types of Heart Failure

1) Left Sided Heart Failure

2) Right Sided Heart Failure

3) Both Sided Heart Failure
Common causes of left sided heart failure are:

1) Ischemic Heart Disease
2) Systemic Hypertension
3) Mitral and Aortic Valve Disease
4) Primary Diseases of Myocardium
Left Sided Heart Failure - Morphology

- Primarily result from progressive damming of blood within the pulmonary circulation and the consequences of diminished peripheral blood pressure and flow
- Findings in the heart depend on the underlying disease
- The left ventricle is usually hypertrophied and dilated, sometimes quite massive
- The extracardiac effects of left sided heart failure are manifested most prominently in lungs
- Changes in Lungs: Pulmonary Congestion and Edema; Lungs will be boggy and heavy.
- There will be interstitial transudate, alveolar septal edema and intra-alveolar edema.
- **Heart Failure Cells:** Capillary leakiness leads to the accumulation of erythrocytes (containing haemoglobin) that are phagocytosed by macrophages. Within macrophages, haemoglobin is converted to haemosidrin-containing macrophages in the alveoli – called Heart Failure Cells
Blood overfills ventricle because of damaged heart muscle.

Blood overflows back into lungs causing pulmonary complications.
Left Sided Heart Failure – Clinical Features

- **Dyspnea (breathlessness):** It is usually the earliest and most significant complaint of patients in left sided heart failure.

- **Cough** is also a common accompaniment, due to fluid transudation into airspaces.

- **Orthopnea:** With further cardiac impairment, patients develop dyspnea when recumbent (so-called Orthopnea); It occurs because of increased venous return from the lower extremities and by elevation of the diaphragm when in supine position.

- Orthopnea is typically relieved by sitting or standing, so that such patients usually sleep while sitting upright.

- **Paroxysmal Nocturnal Dyspnea** is a particularly dramatic form of breathlessness awakening patients from sleep with attacks of extreme dyspnea bordering on suffocation.
Other manifestations of left ventricular failure include:
- Enlarged Heart (Cardiomegaly)
- Tachycardia
- Third Heart Sound (S3)
- Fine rales at the lung bases
- Systolic murmur
- Irregularly irregular heart beat
Right Sided Heart Failure

- **Common Causes of right sided heart failure:**

- **Consequence of Left-Sided Heart Failure (Usual):** Any pressure increase in the pulmonary circulation inevitably produces an increased burden on the right side of the heart.

- **Isolated Right Sided Heart Failure (Less Common):** Seen in:
  - Patients with intrinsic disease of lung parenchyma and/or pulmonary vasculature that result in chronic pulmonary hypertension *(Cor Pulmonale)*
  - Patients with pulmonic or tricuspid valve disease
  - Congenital heart disease with right to left shunt
Right Sided Heart Failure – Morphologic Changes

- The morphologic changes and clinical effects of pure right sided heart failure differ from those of left-sided heart failure in the pulmonary congestion is minimal, whereas engorgement of the systemic and portal venous systems is typically pronounced.

Changes in Liver and Portal System:

- Liver is usually increased in size and weight (Congestive Hepatomegaly).
- Cut section displays prominent passive congestion, a pattern referred to as Nutmeg Liver; Congested red centers of the liver lobules are surrounded by paler, sometimes fatty, peripheral regions.
- In some instances, especially when left-sided heart failure is also present, severe central hypoxia produces Centrilobular Necrosis along with sinusoidal congestion.
- With long standing severe right-sided heart failure, the central areas can become fibrotic, creating so-called Cardiac Fibrosis.
“Nutmeg Liver” in congestive cardiac failure with alternating zones of pale fatty change and dark congestion
Right Sided Heart Failure – Morphologic Changes….. contd

Changes in Spleen

- Right sided heart failure also leads to elevated pressure in the portal vein and its tributaries.

- Congestion produces a tense, enlarged spleen (*Congestive Splenomegaly*).

- Microscopically there can be marked sinusoidal dilatation.

Changes in Pleural & Pericardial Spaces

- Fluid accumulation.

Subcutaneous Tissue

- Peripheral edema of dependent portions of the body, especially ankle (pedal) edema and pretibial edema, is a hallmark of right-sided heart failure.

- Generalized massive edema (*Anasarca*).
Right Sided Heart Failure – Clinical Features

- While the symptoms of left-sided heart failure are largely due to pulmonary congestion and edema, pure right sided heart failure typically causes very few respiratory symptoms.

- There is systemic and portal venous congestion, with hepatic and splenic enlargement, peripheral edema, pleural effusion and ascites.

- In most instances of chronic decompensation, patients present with biventricular congestive cardiac failure, encompassing the clinical syndromes of both right-sided and left sided heart failure.
Diseases of Heart

CONGENITAL HEART DISEASE
Congenital heart diseases are abnormalities of the heart or great vessels that are present at birth.

Arise from faulty embryogenesis during gestational weeks 3 through 8, when major cardiovascular structures develop.

Range from severe anomalies that cause death in the perinatal period to mild lesions that produce minimal symptoms, even in adult life.

CHD either result in shunting of blood between the right and left circulation or cause outflow obstruction.
Pathogenesis of Congenital Heart Diseases

- In at least 80% of cases the cause of CHD is unknown environmental factors, such as maternal viral infections (especially Rubella), chronic maternal alcohol abuse and drugs such as Thalidomide are all clearly related to CHD.

- These factors are of greatest importance between the 4th and 9th weeks of conception. During this period, the common atrial and ventricular chambers are divided by septa, the cardiac valves develop and the primitive truncus arteriosus divides into the aorta and pulmonary artery.

- Some CHD are associated with extracardiac abnormalities and in a small number of these specific chromosomal abnormalities have been detected.
Congenital Rubella Syndrome

- Meningo-encephalitis (7%)
- Glaucoma (3%)
- Cataracts (43%)
- Pigmentary retinopathy (8%)
- Microcephaly (23%)
- Mental retardation (12%)
- Hearing loss (60%)
- Congenital heart disease (PDA: 51%, PS: 18%)
- Hepatosplenomegaly (35%)
- Jaundice (15%)
- Radiolucent bone disease (20%)
- Purpura (37%)
- Thrombocytopenia (34%)
- Other: Low birth weight (57%)
Congenital Heart Diseases - Clinical Features

- Some of the most prominent clinical and pathological features of CHD are:
  - Poor feeding, failure to thrive and impaired growth
  - Respiratory disease or tachpnoea
  - Cyanosis
  - Clubbing
  - Polycythemia (Increased haemoglobin)
  - Cardiac failure
  - Pulmonary hypertension
  - Infective endocarditis

- Most of the children under 1 year of age who present with cardiac failure have a structural abnormality of the cardiovascular system.
Clubbing of Fingers

“Hypertrophyic Osteoarthritis”
Clubbing Fingers and Cyanosis
Cyanosis

Low oxygen levels in the blood cause the lips, fingers, and toes to look blue (cyanotic).
For purpose of discussion, CHDs can be subdivided into three major groups:

(I) Malformations causing a left-to-right shunt

(II) Malformations causing a right-to-left shunt (Cyanotic congenital heart disease)

(III) Malformations causing Obstruction
A **Shunt** is an abnormal communication between chambers or blood vessels.

Depending on pressure relationships, shunts permit the flow of blood from the left heart to the right heart (or vice versa).
Left – to –Right Shunts

- Left-to-right shunts represent the most common type of congenital cardiac malformation.

- Three common lesions included are:
  1) Atrial Septal Defects
  2) Ventricular Septal Defects
  3) Patent Ductus Arteriosus

- Atrial septal defects are typically associated with increased pulmonary blood volumes, while ventricular septal defects and patent ductus arteriosus result in both increased pulmonary blood flow and pressure.

- These malformations can be asymptomatic or can cause fulminant congestive heart failure at birth.
Cyanosis is not an early feature of these defects, but can occur late, after prolonged left–to-right shunting has produced pulmonary hypertension sufficient to yield right–sided pressures that exceed those on the left and thus result in a reversal of blood flow through the shunt.

Such reversal of flow and shunting of unoxygenated blood to the systemic circulation is called *Eisenmenger Syndrome*.

Once significant pulmonary hypertension develops, the structural defects of congenital heart disease are considered irreversible. This is the rationale for early intervention, either surgical or non-surgical.
Congenital Left-To-Right Shunts

A: Atrial Septal Defect (ASD)
B: Ventricular Septal Defect (VSD)
C: Patent Ductus Arteriosus (PDA)
Right – to- Left  Shunts

- Cardiac malformations associated with right-to-left shunt are distinguished by **cyanosis at or near the time of birth.**

- This occurs because poorly oxygenated blood from the right side of the heart is introduced directly into the atrial circulation

- Two lesions are associated with Right-to-left shunts
  1. Fallot Tetrology
  2. Transposition of the Great Vessels
Clinical findings associated with severe long standing cyanosis include clubbing of the finger tips *(Hypertrophic Osteoarthropathy)* and *Polycythemia*.

Right to left shunts permit venous emboli to bypass the lungs and directly enter the systemic circulation *(Paradoxical Embolism)*.
Right to Left Shunts

A: Tetrology of Fallot: Arrow indicates the direction of blood flow.

B: Transposition of Great Vessels with and without VSD.
Obstructive Lesions

- Congenital obstruction to blood flow can occur at the level of:
  - Heart Valves
  - Within a great vessel
  - Within a chamber

- Common examples of congenital obstruction include:
  1. Pulmonic Valve Stenosis
  2. Aortic Valve Stenosis or Atresia
  3. Coarctation of Aorta
# Frequencies of Congenital Cardiac Malformations

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Incidence per Million Live Births</th>
<th>%</th>
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<tbody>
<tr>
<td>Ventricular Septal Defect</td>
<td>4482</td>
<td>42</td>
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<tr>
<td>Atrial Septal Defect</td>
<td>1043</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary Stenosis</td>
<td>836</td>
<td>8</td>
</tr>
<tr>
<td>Patent ductus Arteriosus</td>
<td>781</td>
<td>7</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>577</td>
<td>5</td>
</tr>
<tr>
<td>Coarctation of Aorta</td>
<td>492</td>
<td>5</td>
</tr>
<tr>
<td>Atrioventricular Septal Defect</td>
<td>396</td>
<td>4</td>
</tr>
<tr>
<td>Aortic Stenosis</td>
<td>388</td>
<td>4</td>
</tr>
<tr>
<td>Transposition of Great Arteries</td>
<td>388</td>
<td>4</td>
</tr>
<tr>
<td>Truncus Arteriosus</td>
<td>136</td>
<td>1</td>
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<tr>
<td>Total Anomalous Pulmonary Venous Connection</td>
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<td>1</td>
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<tr>
<td>Tricuspid Atresia</td>
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<tr>
<td><strong>TOTLAL</strong></td>
<td><strong>9757</strong></td>
<td></td>
</tr>
</tbody>
</table>
**Ventricular Septal Defect**

- It is the most common congenital heart disease
- Incomplete closure of the ventricular septum allows left to right shunting
- Most VSD close spontaneously in childhood
- Size ranges from minute defects to large defects involving virtually the entire septum
- In defects associated with a significant left-to-right shunt, the right ventricle is hypertrophied and dilated.
- The diameter of pulmonary artery is increased because of the increased volume ejected by the right ventricle
- Vascular changes typical of pulmonary hypertension are common
Tetrology of Fallot

- Most common cause of Cyanotic Congenital Heart Disease

- The four features of Fallot’s Tetrology are:
  1. VSD
  2. Obstruction to the right ventricular outflow tract (subpulmonic stenosis)
  3. An aorta that overrides the VSD
  4. Right ventricular hypertrophy

- All of these features result from anterosuperior displacement of the infundibular septum, so that there is abnormal division into the pulmonary trunk and aortic root.

- The heart is large and "BOOT SHAPPED" due to right ventricular hypertrophy.

- The proximal aorta is typically larger than normal.
Cynosis is significant

As with any cyanotic heart disease patients develop erythrocytosis with attendant hyperviscosity and hypertrophic osteoarthropathy

Surgical correction is possible in mist of the cases
Coarctation of Aorta

- Coarctation (narrowing or Constriction) of the aorta is a relatively common structural anomaly

- Two classic forms:
  1. **Infantile Form** with hypoplasia of the aortic arch proximal to a PDA
  2. **Adult Form** in which there is a discrete ridge like infolding of the aorta, just opposite the ligamentum arteriosum distal to the arch vessels
Coarctation of Aorta: The area of coarctation is visible as a segmental narrowing of the aorta (arrow)
Diseases of Heart

ISCHEMIC HEART DISEASE
Ischemic Heart Disease is a generic designation for a group of related syndromes resulting from myocardial ischemia – an imbalance between cardiac blood supply (perfusion) and myocardial oxygen demand.

In the vast majority of cases IHD is due to a reduction in coronary blood flow caused by obstructive atherosclerotic disease. Thus IHD is also frequently called Coronary Artery Disease (CAD).

IHD still represents the leading cause of death.
Insufficient blood flow to the heart muscle from narrowing of coronary artery may cause chest pain.
Clinical Syndromes of IHD

- The clinical manifestations of IHD are a direct consequence of insufficient blood supply to the heart.

- There are four basic clinical syndromes of IHD:
  1) Angina Pectoris
  2) Acute Myocardial Infarction
  3) Chronic IHD with CHF
  4) Sudden Cardiac Death

The term Acute Coronary Syndrome is applied to three catastrophic manifestations of IHD: Unstable angina, acute MI and SCD
Angina Pectoris

- Literally means Chest Pain
- In angina ischemia causes pain but is insufficient to lead to death of myocardium
- There is ischemia but no muscle death

Types of Angina:
- **Stable Angina:** Occurs reliably after certain levels of exertion
- **Variant Angina OR Prinzmetal Angina:** Due to vessel spasm
- **Unstable Angina:** Occurring with progressively less exertion or even at rest
Acute Myocardial Infarction

- Severity or duration of ischemia is enough to cause cardiac muscle death
Chronic IHD with CHF

- Progressive cardiac decompensation after acute MI, or secondary to accumulated small ischemic insults, eventually precipitates mechanical pump failure
Sudden Cardiac Death

- Can occur as a consequence of tissue damage from MI, but most commonly results from a lethal arrhythmia without myocyte necrosis.
Ischemic Heart Disease – Epidemiology

1. **Age:** Usually in old age
2. **Sex:** Males are more commonly affected
3. **Major Risk Factors:**
   - Hypertension
   - Diabetes mellitus
   - Smoking
   - Genetic Factors
   - Hyperlipidemia especially LDL
4. **Factors that Might Reduce the Risk of IHD:**
   - Regular Exercise
   - Cessation of Smoking
   - Low Fat Diet
   - Therapeutic and Diagnostic Advances
   - Aspirin Prophylaxis
   - Statins
   - Better arrhythmia control
   - Angioplasty
   - Endovascular stents
   - Thrombolysis
   - Coronary Artery Bypass Surgery
In most cases IHD occurs because of inadequate coronary perfusion relative to myocardial demand. This may result from a combination of preexisting ("fixed") atherosclerotic occlusion of coronary arteries and new superimposed thrombosis and/or vasospasm.

Sequential progression of coronary artery lesion, beginning with stable chronic plaque, responsible for typical angina and leading to the various acute coronary syndromes.
Obstruction of each major coronary artery results in infarction of specific areas of the myocardium

- Although only a single major coronary epicardial artery may be affected by atherosclerotic narrowing, two or all three arteries—Left Anterior Descending (LAD), Left circumflex (LCX), and Right Coronary Artery (RCA)—can be concurrently involved.
Pathogenesis of Ischemic Heart Disease

- Role of Acute Plaque Change
- Role of Inflammation
- Role of Thrombus
- Role of Vasoconstriction
In most patients, unstable angina, infarction and many cases of SCD all occur because of abrupt plaque change followed by thrombosis.

The initiating event is typically disruption of a plaque due to:

- **Rupture**, **Fissuring**, or **Ulceration of Plaque** exposing highly thrombogenic plaque constituents or underlying subendothelial basement membrane
- **Haemorrhage into the Core of Plaques** with expansion of plaque volume and worsening of the luminal occlusion
Role of Inflammation in Ischemic Heart Disease

- Inflammation plays an essential role at all stages of atherosclerosis, from inception to plaque rupture.

- Atherosclerosis begins with the interaction of endothelial cells and circulating leucocytes, resulting in T-cell and macrophage recruitment and activation.

- Inflammatory cells subsequently drive smooth muscle proliferation, with variable amounts of extracellular matrix accumulating over an atheromatous core of lipid, cholesterol, calcification and necrotic debris.

- At later stages, destabilization of atherosclerotic plaque occurs through metalloproteinase secretion from macrophages.
Role of Thrombus in Ischemic Heart Disease

- Thrombosis associated with a disrupted plaque is critical to the pathogenesis of acute coronary syndromes.

- Organizing thrombi produce potent activators for smooth muscle proliferation, which can contribute to the growth of atherosclerotic lesions.
Role of Vasoconstriction in Ischemic Heart Disease

- Vasoconstriction directly compromises lumen diameter

- Vasoconstriction, by increasing local mechanical shear forces, can potentiate plaque disruption

- Vasoconstriction in atherosclerotic plaques can be stimulated by:
  1. Circulating adrenergic agonists
  2. Locally released platelet contents
  3. An imbalance between endothelial cell relaxing factors (e.g., nitric oxide) versus contracting factors (e.g., endothelin)
  4. Mediators released from perivascular inflammatory cells
Angina Pectoris

- **Angina Pectoris** is *intermittent chest pain caused by transient reversible myocardial ischemia*.

- There are three variants:
  1. **Typical OR Stable Angina:**
     - Episodic chest pain *associated with exertion or some other form of increased myocardial oxygen demand.*
     - Crushing or squeezing substernal pain radiating down to left arm or to the left jaw (referred pain)
(2) Prinzmetal OR Variant Angina
- It is angina occurring at rest due to coronary artery spasm
- Etiology is unknown
- Responds promptly to vasodilators like nitroglycerin or calcium channel blockers

(3) Unstable Angina (Crescendo Angina)
- Characterized by increasing frequency of pain, precipitated by progressively less exertion
- The episodes tend to be more intense and longer lasting than stable angina
- Unstable angina is associated with plaque disruption and superimposed partial thrombosis, distal embolization of the thrombus, and/or vasospasm
- Unstable angina is the harbinger of more serious, potentially irreversible ischemia (due to complete luminal occlusion by thrombus) and is therefore sometimes called **Pre-infarction Angina**
Myocardial Infarction

- Myocardial Infarction, popularly called **Heart Attack** is necrosis of heart muscle resulting from ischemia

- One third die even before reaching the hospital

- Frequency increases with increasing age

- Men are at significantly greater risk than women.

- In women menopause and declining estrogen production is associated with exacerbation of atherosclerosis
Myocardial Infarction--- Pathogenesis

- Most MI are caused by acute coronary artery thrombosis.
- In most cases, disruption of an atherosclerotic plaque results in the formation of thrombus.
- Vasospasm and/or platelet aggregation can contribute but are infrequently the sole cause of an occlusion.
Coronary Artery Occlusion

- In a typical MI, following sequence of events transpires:
  - There is sudden disruption of an atheromatous plaque— for example, interplaque haemorrhage, erosion or ulceration, or rupture or fissuring-exposing subendothelial collagen and necrotic plaque contents
  - Platelets adhere, aggregate, become activated, and release potent secondary aggregators including thromboxane A2, adenosine diphosphate and serotonin
  - Vasospasm is stimulated by platelet aggregation and mediator release
  - Other mediators activate the extrinsic pathway of coagulation, adding to the bulk of the thrombus
  - Within minutes the thrombus can evolve to completely occlude the coronary lumen of the coronary vessel
Myocardial Response to Ischemia

- Coronary artery obstruction blocks the myocardial blood supply, leading to ischemia and inadequate ATP production and accumulation of potentially noxious breakdown products like Lactic Acid.
Necrosis begins in a small zone of the myocardium beneath the endocardial surface in the center of the ischemic zone. This entire region of myocardium depends on the occluded vessel for perfusion and is the area at risk. Note that a narrow zone of myocardium immediately beneath the endocardium is spared from necrosis because it can be oxygenated by diffusion from the ventricle. The end result of obstruction to blood flow is necrosis of the muscle that was dependent on perfusion from the coronary artery obstructed. Nearly the entire area at risk loses viability.
Myocardial Infarction-Morphologic Changes

**Distribution of Infarct**

**Left Anterior Descending Artery (40% to 50%):** Artery of Sudden death; Responsible for **Anterior Infarction**; Infarct involves anterior left ventricle, anterior septum and apex circumferentially

**Right Coronary Artery (30% to 40%):** Responsible for **Inferior Infarction**; Involves posterior left ventricle, posterior septum and right ventricular free wall in some cases

**Left Circumflex Artery (15% to 20%):** Responsible for **lateral infarction**; Infarct involves lateral left ventricle except the apex
Based on the size of the involved vessel and the degree of collateral circulation, myocardial infarcts may take one of the following patterns:

- Transmural Infarction
- Subendocardial Infarctions
- Microscopic Infarcts
Myocardial Infarction- Patterns

Transmural Infarct

- Involves the full thickness of the ventricle.
- Are caused by epicardial vessel occlusion through a combination of chronic atherosclerosis and acute thrombosis.
- Yield ST segment elevation and can have a negative Q wave.
Subendocardial Infarct

- Limited to the inner third of the myocardium.
- Do not yield ST segment elevation or Q waves.
Myocardial Infarction - Patterns

Microscopic Infarct

- Occurs in the setting of small vessel occlusions.
- May not show any diagnostic ECG changes.
Dependence of myocardial infarction on the location and mature of the diminished perfusion

**LEFT:** Patterns of transmural infarction resulting from major coronary artery occlusion

**RIGHT:** (TOP) Patterns of infarction resulting from partial or transient occlusion; (MIDDLE) Global hypotension superimposed on fixed three-vessel disease; (BOTTOM) Occlusion of small intra-myocardial vessels
Factors influencing MI

- Site, size, rate of development of AS
- Size of vascular bed
- Duration
- Myocardial demands
- Collateral circulation
- Coronary artery spasm
- BP, HR, cardiac rhythm
<table>
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<tr>
<th>TIME</th>
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<tr>
<td>0 – ½ hr</td>
<td>-----</td>
<td>Myofibril relaxation; Swelling of mitochondria</td>
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<tr>
<td>½ - 4 hr</td>
<td>-----</td>
<td>Wavy fibers at borders</td>
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<tr>
<td>4 – 12 h</td>
<td>Occasional dark mottling</td>
<td>Coagulation Necrosis, Edema; Haemorrhage</td>
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<tr>
<td>12-24 h</td>
<td>Dark mottling</td>
<td>Necrosis; Pyknosis; Myocyte eosinophilia; Contraction bands, Neutrophils</td>
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<td>Time Frame</td>
<td>Morphologic Changes</td>
<td>Pathologic Changes</td>
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<tr>
<td>1 - 3 days</td>
<td>Mottling + Yellow centre</td>
<td>Loss of nuclei &amp; striations, Neutrophils ++</td>
</tr>
<tr>
<td>3 - 7 days</td>
<td>Red border, yellow tan center</td>
<td>Disintegration; Phagocytosis</td>
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<tr>
<td>7 - 10 days</td>
<td>Max yellow soft center, red borders</td>
<td>Phagocytosis ++, Granulation tissue at margins</td>
</tr>
<tr>
<td>10 - 14 days</td>
<td>Red-gray depressed</td>
<td>Granulation tissue ++; Collagen +</td>
</tr>
<tr>
<td>2 - 8 wks</td>
<td>Grey white scar</td>
<td>↑ collagen, ↓ cellularity</td>
</tr>
<tr>
<td>&gt; 2 month</td>
<td>Complete scar</td>
<td>Dense Collagenous scar</td>
</tr>
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</table>
Acute Myocardial Infarct of the Posterolateral Left Ventricle
One day old infarct showing coagulative necrosis along with wavy fibers, compared with adjacent normal fibers (at right). Widened spaces contain edema fluid and scattered neutrophils.
The earliest change histologically seen with acute myocardial infarction in the first day is contraction band necrosis. The myocardial fibers are beginning to lose cross striations and the nuclei are not clearly visible in most of the cells seen here. Note the many irregular darker pink wavy contraction bands extending across the fibers.
This high power microscopic view of the myocardium demonstrates an infarction of about 1 to 2 days in duration. The myocardial fibers have dark red contraction bands extending across them. The myocardial cell nuclei have almost all disappeared. There is beginning acute inflammation. Clinically, such an acute myocardial infarction is marked by changes in the electrocardiogram and by a rise in the MB fraction of creatine kinase.
Dense Neutrophilic infiltrate in area of two to three days old Myocardial Infarction
This myocardial infarction is about 3 to 4 days old. There is an extensive acute inflammatory cell infiltrate and the myocardial fibers are so necrotic that the outlines of them are only barely visible.
Myocardial Infarction - 7 to 10 Days Old

Nearly complete removal of necrotic myocytes by macrophage phagocytosis
This is an intermediate myocardial infarction of 1 to 2 weeks in age. Note that there are remaining normal myocardial fibers at the top. Below these fibers are many macrophages along with numerous capillaries and little collagenization.
Granulation tissue characterized by loose collagen and abundant capillaries
Well-healed myocardial infarct with replacement of the necrotic fibers by dense collagenous scar. A residual cardiac muscle cells are present.
Fig A: Normal Myocardium

Fig B: Myocardium with coagulation necrosis (upper two thirds of figure), showing strongly eosinophilic anucleate myocardial fibers. Leucocytes in the interstetium are an early reaction to necrotic muscle. Compare with A and with normal fibers in the lower part of figure.
Changes in an Infarct due to Reperfusion

- The current therapeutic goal in acute MIs is to salvage the maximal amount of ischemic myocardium by restoration of tissue perfusion as quickly as possible.

- Such reperfusion is achieved by thrombolysis (dissolution of thrombus by streptokinase or tissue plasminogen activator), balloon angioplasty (with or without stenting), or coronary artery by pass graft.
Consequences of Myocardial Ischemia Followed by Reperfusion

A: **Gross Appearance**: Large haemorrhagic, anterior wall MI from patient treated with streptokinase

B: **Microscopic Appearance**: Myocardial necrosis with haemorrhage and contraction bands
Clinical Diagnosis is based on:

1. Symptoms
2. ECG Changes
3. Elevation of Specific Serum Enzymes (Cardiac Enzymes)
Myocardial Infarction - Symptoms

- Onset is severe with chest constricting, crushing, burning substernal or precordial pain that radiates to the left shoulder and arm or jaw

- Pain is accompanied by sweating, nausea, vomiting or dyspnea

- Cardiogenic shock: In massive MI when more than 40% of left ventricle is involved.

- Chest pain may be absent in 20-40% of patients with diabetes and hypertension or in old patients
Symptoms of Angina

Angina can spread anywhere between the belly button and the jaw, including to the shoulder, arm, elbow or hand—usually on the left side.
ST Segment Elevation, followed by abnormal new Q waves and inverted T wave
ST Segment Elevation

- 1 mm above baseline (limb)
- 2 mm above baseline (chest)
- 0.08 sec to right of J point

Look for in two or more leads facing same area
Post Myocardial Infarction

Hyperacute phase

Fully evolved phase

Resolution phase

Stabilized chronic phase
Laboratory evaluation of MI is based on measuring the blood levels of intracellular macromolecules that leak out of injured myocardial cells through damaged cell membranes.

These include:

- Cardiac Troponins T and I (TnT,TnI)
- Creatine Kinase (CK, and more specifically the myocardial specific isoform, CK-MB)
- Lactate Dehydrogenase (LDH)
- SGOT
- Myoglobin and others

Tropinins and CK-MB have high specificity and sensitivity for myocardial damage.
Myocardial Infarction- Laboratory Evaluation... contd

- TnI and TnT are not normally detectable in the circulation, but after acute MI both troponins become detectable after 2 to 4 hours and peak at 48 hours; their levels remain elevated for 7 to 10 days.

- CK-MB is the second best marker after troponins. Begins to rise within 2 to 4 hours of MI, peaks at 24 to 48 hours, and returns to normal within 72 hours.
Cardiac enzyme changes with MI

- **Lactate dehydrogenase**
- **Troponin**
- **Creatine Kinase**

**Graph:**
- **Y-axis:** Enzyme level increase above normal
- **X-axis:** Time (days)
- **Legend:**
  - Blue line: Lactate dehydrogenase
  - Red line: Troponin
  - Green line: Creatine Kinase

**Timeline:**
- Onset of chest pain
- 1 to 14 days
Changes in Serum Enzymes in MI

- CK-MB rises rapidly. And returns to baseline rapidly
- LDH is the test of choice from 2 to 7 days
- AST lacks specificity, as present in high concentration in liver and skeletal muscles
Complication of MI:

- Contractile dysfunction $\rightarrow$ cardiogenic shock
- Arrhythmias
- Myocardial Rupture $\rightarrow$ cardiac rupture syndrome
- Pericarditis
- Infarct Expansion
- Mural thrombus
- Ventricular aneurysm
- Papillary muscle dysfunction
- Progressive late heart failure
Complications of Myocardial Infarction

A: Anterior Myocardial Rupture
B: Rupture of Ventricular Septum
C: Complete rupture of a necrotic papillary muscle
D: Fibrinous Pericarditis
E: Early expansion of anteroapical infarct with wall thinning (arrow) and mural thrombus
F: Large apical left ventricular aneurysm (arrow)
Chronic Ischemic Heart Disease

- Also called Ischemic Cardiomyopathy

- Essentially progressive heart failure as a consequence of ischemic myocardial damage

- In most instances there is a history of Myocardial Infarction

- Chronic IHD results from post infarction cardiac decompensation that follows exhaustion of the hypertrophy of the viable myocardium

- In other cases severe obstructive CAD may be present without prior infarction, but with diffuse myocardial dysfunction
Chronic Ischemic Heart Disease - Morphology

- Heart is enlarged and heavy from left ventricular dilatation and hypertrophy
- Moderate to severe atherosclerosis of coronary arteries
- Discrete gray-white scars of healed infarcts are usually present
- The major microscopic findings include myocardial hypertrophy, diffuse subendocardial vacuolization and fibrosis from previous infarcts
Chronic Ischemic Heart Disease - Clinical Features

- Chronic IHD is characterized by development of severe, progressive heart failure, sometimes punctuated by episodes of angina or MI.

- Arrhythmias are common and, along with CHF and intercurrent MI, account for many deaths.
Sudden Cardiac Death

- Sudden Cardiac Death (SCD) is defined as unexpected death from cardiac causes either without symptoms or within 1 to 24 hours of symptom onset.

- Coronary artery disease is the most common underlying cause of SCD.

- In many adults SCD is the first clinical manifestation of IHD.
With younger victims of SCD other nonatherosclerotic causes are more common including:

- Hereditary or acquired abnormalities of cardiac conduction system
- Congenital coronary arterial abnormalities
- Mitral valve prolapse
- Myocarditis or Sarcoidosis
- Dilated or Hypertrophic Cardiomyopathy
- Pulmonary Hypertension
- Myocardial hypertrophy. Increased cardiac mass is an independent risk factor for SCD; thus, in some young persons who die suddenly, including athletes, hypertensive hypertrophy or unexplained increased cardiac mass is the only pathologic finding

The ultimate mechanism of Sudden Cardiac Death is most often a lethal arrhythmia, such as Ventricular Fibrillation
Pathway in the progression of Ischemic heart Disease

1. CORONARY ARTERY DISEASE
   - Myocardial ischemia
   - Acute plaque change; coronary artery thrombosis
   - Myocardial ischemia of increased severity and duration

2. MYOCARDIAL INFARCTION with muscle loss and arrhythmias
   - Infarct healing
   - Ventricular remodeling
   - Hypertrophy, dilation of viable muscle

3. Chronic ischemic heart disease

4. Congestive heart failure

5. SUDDEN CARDIAC DEATH
# Myocardial Infarction - Summary

## Etiology
Caused by vasospasm, embolus, or atherosclerotic thrombus resulting in coronary artery occlusion. Risk factors include increasing age, smoking, diabetes, male gender, post menopausal women and hyperlipidemia.

## Pathology
Heart: Progression from wavy fibers with edema and haemorrhage (4-12 hours) to coagulative necrosis with muscle hypereosinophilia and neutrophilic infiltration (12-36 hours) to macrophages infiltration with phagocytosis of dead cells and formation of granulation tissue (5-10 days) to scar formation (10 days to 2 months).

## Clinical Manifestations
Crushing, substernal chest pain with radiation to jaw and left arm; associated symptoms include dyspnea, nausea and diaphoresis.
Complications include Cardiac arrhythmia (can cause sudden within first few days), fibrinous pericarditis (within 3-5 days), congestive heart failure, shock, thromboembolism, rupture of ventricular free wall or septum (VSD) (within 7-10 days), rupture of papillary muscle leading to mitral regurgitation and Dressler syndrome (autoimmune fibrinous pericarditis several weeks post MI).
Lab Findings: Elevated cardiac Troponin (seen within 4 hours to 10 days); elevated CK-MB, LDH-1 and AST; ECG: STEMI is diagnosed acutely with ST elevation; non-STEMI may present with inverted T waves or ST depressions. Eventually, Q waves may develop for both STEMI and non-STEMI.

## Treatment
Thrombolytic therapy or coronary angioplasty for STEMI. Coronary angioplasty or medical treatment for non-STEMI; Medical therapy with aspirin, statins, β - blockers and smoking cessation for all myocardial infarctions.
Diseases of Heart

VALVULAR HEART DISEASE
Valvular Heart Disease

- At least 10% of cases of heart failure are caused by disease of cardiac valves.

- The normal function of cardiac valves is to prevent retrograde flow of blood between the atria and ventricles, and between the ventricles and the aorta or pulmonary artery.

- Valves open noiselessly but heart sounds are produced by the vibration of blood as valve closes.

- Abnormal flow through diseased valves typically produces abnormal heart sounds called murmurs.
Pathologic problems in valves result from:

Valve Stenosis, in which valve become thickened or calcified and obstruct the normal flow of blood into a chamber or vessel.

Valve Incompetence (also called Regurgitation or Insufficiency), in which valves lose their normal function as valves fail to prevent the reflux of blood after contraction of an individual cardiac chamber.

Vegetations, in which the valve leaflets develop either infective or thrombotic nodules that impair normal valve mobility and can fragment and embolize.
Common Valvular Diseases

- Calcific Aortic Stenosis
- Myxomatous Mitral Valve
- Rheumatic Valvular Disease
- Infective Endocarditis
- Noninfected Vegetations
- Carcinoid Heart Disease
- Prosthetic Cardiac Valves
# Pathological Causes and Clinical Features of Mitral & Aortic Valvular Lesions

<table>
<thead>
<tr>
<th>VALVULAR LESION</th>
<th>PATHOLOGICAL CAUSE</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MITRAL STENOSIS</strong></td>
<td>Rheumatic Fever</td>
<td>Pulmonary hypertnension; Left atrial and right ventricular hypertrophy; Opening snap and diastolic murmur</td>
</tr>
<tr>
<td><strong>MITRAL INCOMPETENCE</strong></td>
<td>Rheumatic Fever, Dilatation of mitral annulus, Papillary muscle fibrosis and dysfunction, Mucoid degeneration of valve cusps (mitral valve prolapse)</td>
<td>Variable haemodynamic effects, Pansystolic murmur, Mid-systolic click and late systolic murmur in mitral prolapse</td>
</tr>
<tr>
<td><strong>AORTIC STENOSIS</strong></td>
<td>Calcific Degeneration, Rheumatic Fever</td>
<td>Ejection systolic murmur, Left Ventricular hypertrophy, Angina, syncope, left ventricular failure or sudden death</td>
</tr>
<tr>
<td><strong>AORTIC INCOMPETENCE</strong></td>
<td>Rheumatic Fever, Dilatation of aortic root (age related or syphilitic), Some rheumatological disorders, e.g. rheumatoid arthritis, ankylosing spondylitis</td>
<td>Diastolic Murmur, Wide pulse pressure, collapsing pulse, angina, left ventricular failure</td>
</tr>
</tbody>
</table>
Diseases of Heart

RHEUMATIC HEART DISEASE
Rheumatic Valvular Disease OR Rheumatic Heart Disease

- An acute, immunologically mediated multisystem inflammatory disease

- Occurs a few weeks after an episode of Group A – β Haemolytic Streptococcal pharyngitis (Post Streptococcal Disease)

- Acute Rheumatic Heart Disease (RHD) is the cardiac manifestation of rheumatic fever and is associated with inflammation of the valves, myocardium, or pericardium

- Chronic valvular deformities are the most important consequences of RHD

- Valvular lesions of RHD are characterized by diffuse and dense scarring of valves resulting in permanent dysfunction (Mitral Stenosis being most common)
In economically depressed urban areas or developing countries, RF and RHD remain important public health problems.

Decline in developed world can be ascribed to:
- Improved socioeconomic conditions
- Rapid diagnosis
- Rapid treatment of streptococcal pharyngitis
- Fortuitous (and unexplained) decline in the virulence of group A streptococcus
Rheumatic Valvular Disease - Pathogenesis

- Acute Rheumatic fever is an immunological reaction induced by group A streptococcal

- Antibodies directed against the *M-Protein* of group A *Streptococci* cross react with the tissue glycoproteins in the heart, joints, and other tissues and produce inflammation of these tissues

- The onset of symptoms 2-3 weeks after infection and the absence of streptococci from the lesion support the concept that rheumatic fever results from an immune response against the offending bacteria
Group A Streptococcal Pharyngitis

Formation of Antibodies Against M-Protein of Bacteria

Antibodies React Against Bacteria

*But*

Cross React With Normal Body Tissues

- Cross React With Heart Valvular Tissue
  - Rheumatic Valvular Disease
- Cross React With Glomerular Tissue
  - Glomerulonephritis
- Cross React With Articular Tissue
  - Arthritis
Pathogenesis and Morphologic Changes of Acute Rheumatic Disease

- Acute Rheumatic Fever causes changes in the endocardium, myocardium and epicardium.

- Chronic rheumatic heart disease is almost always caused by deformity of the heart valves, particularly the mitral and aortic valves.
Rheumatic Valvular Disease - Morphologic Changes

Aschoff Bodies:
- During acute rheumatic fever, discrete inflammatory lesions are found in various tissues throughout the body.
- Within the heart, these are called Aschoff Bodies and are pathognomonic for RF.
- These are comprised of a central zone of degenerating, hypereosinophilic extracellular matrix infiltrated by lymphocytes (primarily T-cells), occasional plasma cells, and plump activated macrophages called Antischow Cells.

Antischow Cells
- Antischow cells have abundant cytoplasm and central nuclei with chromatin arrayed in a slender, wavy ribbon (so-called Caterpillar Cells).

- Macrophages can fuse to form Giant Cells.
- Aschoff bodies can be found in any of the three layers of heart - pericardium, endocardium or myocardium - so called Pencarditis.
Microscopic appearance of an Aschoff Body in a patient with acute rheumatic carditis. There is central necrosis with a circumscribed collection of inflammatory cells, with some activated macrophages (Antischow cells) with prominent nucleoli (arrow heads).
Here is an Aschoff nodule at high magnification. The most characteristic component is the Aschoff giant cell. Several appear here as large cells with two or more nuclei that have prominent nucleoli. Scattered inflammatory cells accompany them and can be mononuclears or occasionally neutrophils.
Another peculiar cell seen with acute rheumatic carditis is the Anitschkow myocyte. This is a long, thin cell with an elongated nucleus.
Aschoff Body with central granular or hyaline debris with large mononuclear cells, some with multiple nuclei
Valvular involvement results in fibrinoid necrosis along the lines closure, forming 1 to 2 mm vegetations called **Verrucae**
Chronic Rheumatic Heart disease is characterized by organization of the acute inflammation and subsequent scarring.

The cardinal anatomic changes of the mitral (or tricuspid) valve include leaflet thickening and fusion and shortening, and thickening and fusion of chordae tendineae.

Fibrous bridging across the valvular commissures and calcification create Fish Mouth OR Button Hole stenoses.

Aschoff bodies are replaced by fibrous scar.
Chronic Rheumatic Heart Disease

Mitral stenosis with diffuse fibrous thickening and distortion of the valve leaflets
Surgically removed specimen of rheumatic aortic stenosis demonstrating thickening and distortion of the cusps with commissural fusion
Clinical Features For the Diagnosis of Rheumatic Fever (Jones Criteria)

<table>
<thead>
<tr>
<th>MAJOR CRITERIA</th>
<th>MINOR CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyarthritis (75%)</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Carditis (35%)</td>
<td>Fever (75%)</td>
</tr>
<tr>
<td>Chorea (10%)</td>
<td>Preceding bout of rheumatic fever</td>
</tr>
<tr>
<td>Subcutaneous Nodules (10%)</td>
<td>Elevated ESR OR C-Reactive Protein</td>
</tr>
<tr>
<td>Erythema Marginatum (10%)</td>
<td>Prolonged PR Interval on ECG</td>
</tr>
</tbody>
</table>

A diagnosis of Rheumatic Fever is made when patient has: Two Major Criteria OR One Major and Two Minor Criteria
IS IT RHEUMATIC FEVER?

Strep Throat

Rheumatic Fever

Rheumatic Heart Disease

If you experience any of these symptoms, SEE YOUR DOCTOR!
Chorea

Random involuntary movements (chorea) are caused by involvement of the basal ganglia of brain
Rheumatic Fever - Investigations

- Diagnosis is usually clinical.
- Following investigations may be helpful

1. **Evidence of Systemic Disease** e.g.
   - Raised ESR
   - Leucocytosis

2. **Evidence of Preceding Streptococcal Infection**
   - Throat swab culture for group A Streptococci
   - Antistreptolysin O antibodies titer (ASO Titer) - High titer indicates recent streptococcal infection

3. **Evidence of Carditis**
   - Chest X-Ray may show cardiac enlargement or pulmonary congestion
   - ECG may show features of heart block and pericarditis
   - Echocardiography is performed when valve abnormality is suspected
### Etiology

**Acute Rheumatic Fever:** Antibodies formed against *Group A- β –Haemolytic Streptococci* cross react against patient’s tissues; usually presents in children 5-15 years of age  
**Rheumatic Heart Disease:** Late sequalae of acute rheumatic fever; presents 20+ years after Acute Rheumatic fever

### Pathology

**Acute Rheumatic Fever:** Presence of Aschoff bodies (inflammatory foci surrounded by lymphocytes) and Anitschkow Cells (macrophages that may become multinucleated) producing a pancarditis in heart tissue; serofibrinous pericardial exudate  
**Rheumatic Heart Disease:** Mitral stenosis with fish-mouth deformity; may also affect aortic valve

### Clinical Manifestations

**Acute Rheumatic Fever:** Onset of symptoms 2-3 weeks after streptococcal pharyngitis; major Jones criteria include carditis, migratory polyarthritis, chorea, erythema marginatum (blanching, ring-shaper rash) and subcutaneous nodules; minor Jones criteria included fever, arthralgia, or evidence of previous streptococcal infection (positive ASO titer); Lab findings: Elevated ESR  
**Rheumatic Heart Disease:** Presents with valvular heart disease (usually mitral stenosis, but may have aortic stenosis as well); valvular disease may lead to hypertrophy of heart, arrhythmias and heart failure

### Treatment

**Acute Rheumatic Fever:** Penicillin for streptococcal infection; salicylates for fever and arthritis  
**Rheumatic Heart Disease:** Endocarditis prophylaxis if indicated; valve replacement when indicated for severe symptomatic valvular disease
Diseases of Heart

INFECTIVE ENDOCARDITIS
Infective Endocarditis

Infective Endocarditis is an infection associated with formation of vegetations on the endocardial surface, usually on a valve.
Risk Factors and Infective Agents For Infective Endocarditis

(1) Preexisting Cardiac Abnormalities
- Chronic Rheumatic Heart Disease
- Mitral Valve Prolapse
- Congenital Heart Diseases

Organisms
- Streptococci 50-60% (S. Viridans, S. Faecalis)
- Staphylococci 10-25% (S. aureus, S. Epidermidis)

(2) Prosthetic Heart Valves (Valve Replacement)

Organisms
- Staphylococcus Epidermidis 50%
- Gram Negative Bacilli 15%
- Candida (fungus) 15%

(3) Intravenous Drug Abuse

Organisms
- Staphylococcus Aureus (most common)
- Streptococcal Viridans
- Gram Negative Bacilli
- Candida
Infective Agents For Infective Endocarditis

- Streptococci (29%)
- Staphylococci (42%)
- Enterococci (11%)
- Fungi (2%)
- Culture negative organisms (8%)
- Polymicrobial (1%)
- HACEK (2%)
- Gram(-) rods (2%)
Infected Endocarditis- Types

1. ACUTE INFECTIVE ENDOCARDITIS

2. SUBACUTE INFECTIVE ENDOCARDITIS
Acute Infective Endocarditis

- Caused by organisms of high virulence such as *staphylococcus aureus*, which frequently infect previously normal valves

- The condition is characterized by severe destruction of valve resulting in acute valvular regurgitation

- There is severe bacteremia associated with abscesses in the myocardium and throughout the body
Subacute Infective Endocarditis

- Caused by organisms of low virulence such as streptococcus viridans and staphylococcus epidermidis

- Almost always occur in patients with a preexisting valvular abnormality

- This condition has more chronic course and is not characterized by severe valve destruction or abscess formation
# Acute VS Sub Acute Infective Endocarditis

<table>
<thead>
<tr>
<th>Acute Infective Endocarditis</th>
<th>Subacute Infective Endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually occurs on previously normal valves</td>
<td>Mostly underlying cardiac disease present</td>
</tr>
<tr>
<td>Caused by highly virulent organism, e.g., Staphylococcus Aureus</td>
<td>Caused by organism of relatively low virulence. Many of these are commensals and get entry into blood following surgical procedures, e.g., Streptococcus Viridans</td>
</tr>
<tr>
<td>Rapidly progressive</td>
<td>Insidious Course</td>
</tr>
<tr>
<td>A well defined extra cardiac focus of infection is often present providing source of bacteremia</td>
<td>A well defined infection elsewhere is seldom identified. Bacteremia may originate from focus of dental surgery, catheterization of urinary bladder, etc</td>
</tr>
</tbody>
</table>
Infective Endocarditis

Two factors are essential in the pathogenesis of infective endocarditis:

1. Bacteremia

2. Abnormality in the endothelial surface that permits bacterial entry and multiplication with a highly virulent agent such as Staphylococcus aureus. Infection may occur with a minor, inapparent endocardial injury with less virulent agents. Preexisting endocardial abnormality exists, most commonly chronic rheumatic valve disease.
Formation of vegetations on a valve leaflet in infective endocarditis

A: A focal area of abnormality on the endocardium of a valve leaflet is covered with tiny deposits of platelets and fibrin; this is in effect the beginning of a thrombus

B: Circulating microorganisms (released into blood stream) colonise the platelet thrombus

C & D: When sufficient bacteria have settled, further blankets of platelets ad fibrin are laid down. The bacteria proliferate slowly to form colonies occupying a relatively superficial position in the vegetation. They are separated from the blood stream by a thin layer of fibrinous material. This layer prevents the phagocytes reaching the bacteria, but is not a significant barrier to the diffusion of nutrients from the blood stream.
Infective Endocarditis-Morphologic Changes

- The hallmark of infective endocarditis is the presence of **Valvular Vegetations** containing bacteria or other organism. Vegetations are thrombi on endocardium formed with fibrin and platelets and containing causative microorganism. The organisms within the vegetations are relatively protected from host defense because the valves are avascular which limits access of leucocytes or antimicrobial substances.

- The vegetations of infective endocarditis are multiple, large and friable and commonly become detached from the valve as emboli. Vegetations tend to be larger and more friable in acute than in subacute endocarditis.
<table>
<thead>
<tr>
<th>Acute Infective Endocarditis</th>
<th>Subacute Infective Endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetations bulkier than of subacute</td>
<td>Vegetations are relatively small</td>
</tr>
<tr>
<td>Vegetations more often occur on previously normal valves, cause perforation of the underlying valve leaflet</td>
<td>Vegetations are generally superimposed on previously damaged valves</td>
</tr>
</tbody>
</table>
The vegetations cause rapid destruction of the valves, often resulting in rupture of the leaflets, chordae tendinae or papillary muscles. The infection may extend through the valve into the adjacent myocardium to produce abscesses in the perivalvular tissue, termed Ring Abscess.

Systemic emboli may occur due to friable nature of the vegetations and may cause infarcts in brain, kidney, myocardium and other tissues. Because the emboli contain large number of virulent organisms, abscesses develop at the sites of such infarcts.
**A:** Endocarditis of mitral valve (subacute, caused by streptococcus viridans)

The large, friable vegetations are denoted by arrows

**B:** Subacute endocarditis of congenitally bicuspid aortic valve (caused by Staphylococcus Aureus) with extensive cuspal destruction and ring abscess (arrow)
Vegetations in Endocarditis showing perforation
Infective Endocarditis - Clinical Features

- **Features of Bacteremia**
  1. **Fever:** Low grade fever with malaise and weight loss in subacute endocarditis while the high grade fever and shaking chills in acute endocarditis
  2. **Splenomegaly:** Due to endothelial hyperplasia caused by chronic bacteremia
  3. **Petchial Haemorrhages:** Haemorrhage in the skin, retina and nails (splinter haemorrhages) develop due to bacteremia
  4. **Milliary Abscess:** In all organs of body in acute endocarditis

- **Features of Immune Complexes**
  Antibodies and bacterial antigens combine to form circulating immune complexes. Deposition of these immune complexes develop the following features
  1. **Glomerulonephritis**
  2. **Janeway Lesions:** Erythematous papules in the palm and sole
  3. **Osler’s Nodes:** Tender red nodules in the fingers or toes
Infective Endocarditis- Clinical Features..... contd

Features of Valvular Dysfunction

1. Murmurs: Due to vegetations which hinder the flow of blood, producing turbulence and therefore abnormal heart sounds (murmurs)

2. Regurgitation: Progressive destruction of the valve may produce valve perforation and regurgitation

Features of Embolism

Emboli from the friable vegetations are common producing the following features:

- Infarction: With left sided endocarditis, systemic embolism causes multifocal areas of infarction in the brain, kidney, heart, intestine, spleen and extremities. With right sided endocarditis, embolism involves the pulmonary vessels

2. Mycotic Aneurysms: In about 10% of cases, the organism in the embolus produces a local infection in the artery at the site of lodgment, causing weakening of the arterial wall and formation of an aneurysm. This aneurysm caused by infection is called mycotic aneurysm.
Complications of Infective Endocarditis

- Bronchopneumonia
- Pulmonary infarct
- (Tricuspid valve endocarditis)
- Myocarditis
- Renal infarcts
- Glomerulonephritis
- Splenomegaly ± infarcts
- Anaemia
- Haematuria
- Splinter haemorrhages
- Clubbing
Complications of Infective Endocarditis

- Cerebral emboli (15%)
- Roth's spots (rare, <5%)
- Subconjunctival haemorrhages (2-5%)
- Petechial haemorrhages on mucous membrane and fundus (20-30%)
- Splenomegaly (30-40%, longstanding endocarditis only)
- 'Varying' murmurs (60% new or pre-existing murmurs, 15-30% new or changed murmurs)
- Conduction disorders (10-20%)
- Cardiac failure (40-50%)
- Haematuria (60-70%)
- Digital clubbing (10%, longstanding endocarditis only)
- Splinter haemorrhages (10%)
- Osler's nodes (5%)
- Petechial rash (40-50%, may be transient)
- Loss of pulses
- Clubbing (10%, longstanding endocarditis only)
- Janeway's spots
- Splinter haemorrhages (10%)

Systemic emboli (7%)
Changes in the hands & Nails in Infective Endocarditis

A: Prominent splinter haemorrhages

B: Normal nail beds

C: Clubbing in infective endocarditis. This is sometimes known as Schamroth’s Sign.

Causes of Clubbing

1. Congenital Heart Diseases
2. Infective Endocarditis
3. Bronchogenic carcinoma
4. Bronchiactasis
Seen here in the finger at the right are small splinter hemorrhages in a patient with infective endocarditis. These hemorrhages are subungual, linear, dark red streaks. Similar hemorrhages can also appear with trauma.
Another small linear splinter hemorrhage is seen here subungually on the left thumb of a patient with infective endocarditis and blood culture positive for Staphylococcus aureus.
**Echocardiographic appearance of valve vegetations:** In this case the vegetations are on the tricuspid valve (arrow). The patient was an intravenous drug user.
Infective Endocarditis - Investigations

1. **Repeated Blood Culture**: to identify microorganisms

2. **Complete Blood Picture**: It may show anemia, leucocytosis and thrombocytosis

3. **ESR**: Raised

4. **Echocardiography**: To identify vegetations, valve damage and abscess formation

5. **Chest-X Ray**: It may show cardiomegaly and heart failure
Comparison of the lesions in the four major forms of vegetative endocarditis

**Rheumatic Heart Disease:** Marked by a row of small, warty verrucae along the lines of closure of the valve leaflets

**Infective Endocarditis:** Typically shows large, irregular and destructive masses that can extend onto chordae

**Nonbacterial Thrombotic Endocarditis:** Typically shows small, bland vegetations, usually attached at the line of closure

**Libman-Sacks Endocarditis:** Has small or medium-sized vegetations on either or both sides of the valve leaflets
# Acute And Subacute Endocarditis

## Etiology

**Acute:** Often caused by *Staphylococcus aureus*

**Subacute:** Often caused by (e.g., *streptococcus mutans*); often occurs after dental procedures

*viridans streptococci*

## Pathology

**Acute:** Larger vegetations consisting of fibrin, inflammatory cells and bacteria on previously normal valves

**Subacute:** Small vegetations consisting of fibrin, chronic inflammatory cells and fibrosis on abnormal valves

## Clinical Manifestations

**Acute:** Sudden high fever with chills; new onset of murmur

**Subacute:** Insidious onset with low grade fever

Both types can present with Osler nodes (painful nodules on digit pads), Janeway lesions (red rash on palms and soles), Roth spots (white spots on retina with surrounding hemorrhage), nail-be splinter haemorrhages and bacterimia

Complications include chordae tendinea rupture, perforation of valvular leaflet, heart failure, suppurative pericarditis, mycotic aneurysms and septic emboli to lung, spleen, kidneys, heart or brain

## Treatment

**Acute:** Broad spectrum antibiotics, may need surgical treatment if severe

**Subacute** Broad-spectrum antibiotics; prophylaxis of SBE with antibiotics in susceptible individuals before dental procedures

## Notes

Tricuspid valve endocarditis is associated with IV drug use; Non bacterial endocarditis is associated with sterile emboli and seen with cancer metastasis or renal failure (marentic endocarditis), SLE (Libman-Sacks endocarditis, which demonstrates vegetations on both side of valves), DIC or carcinoid syndrome
This diagram depicts the appearance of a serous pericarditis. The amount of inflammation is minimal, so no exudation of fibrin occurs. The dark stippled dots in the yellow fluid and on the epicardial surface represent scattered inflammatory cells. Serous pericarditis is marked by fluid collection. Rarely, the fluid collection may be large enough to cause tamponade.
This diagram depicts the appearance of a fibrinous pericarditis. The red-pink squiggly
This is an example of a fibrinous pericarditis. The surface appears roughened from the ...
This high power microscopic appearance of cardiac myxoma shows minimal cellularity. Only scattered spindle cells with scant pink cytoplasm are present in a loose myxoid stroma.
This portion of aorta was resected from a patient with a coarctation. The aorta narrows postductally here to about a 3 mm opening.
Here is a large, dilated left ventricle typical of a dilated, or congestive, cardiomyopathy.
Microscopically, the heart in cardiomyopathy demonstrates hypertrophy of myocardial fibers along with interstitial fibrosis.
The left ventricle is markedly thickened in this patient with severe hypertension that