BLOOD VESSELS

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Blood Vessels

- (1) Large Elastic Arteries(aorta, inominate)
- (2) Medium sized muscular Arteries(coronary, renal)
- (3) Small arteries
- (4) Arterioles
- (5) Capillaries
- (6) Venules --- Veins

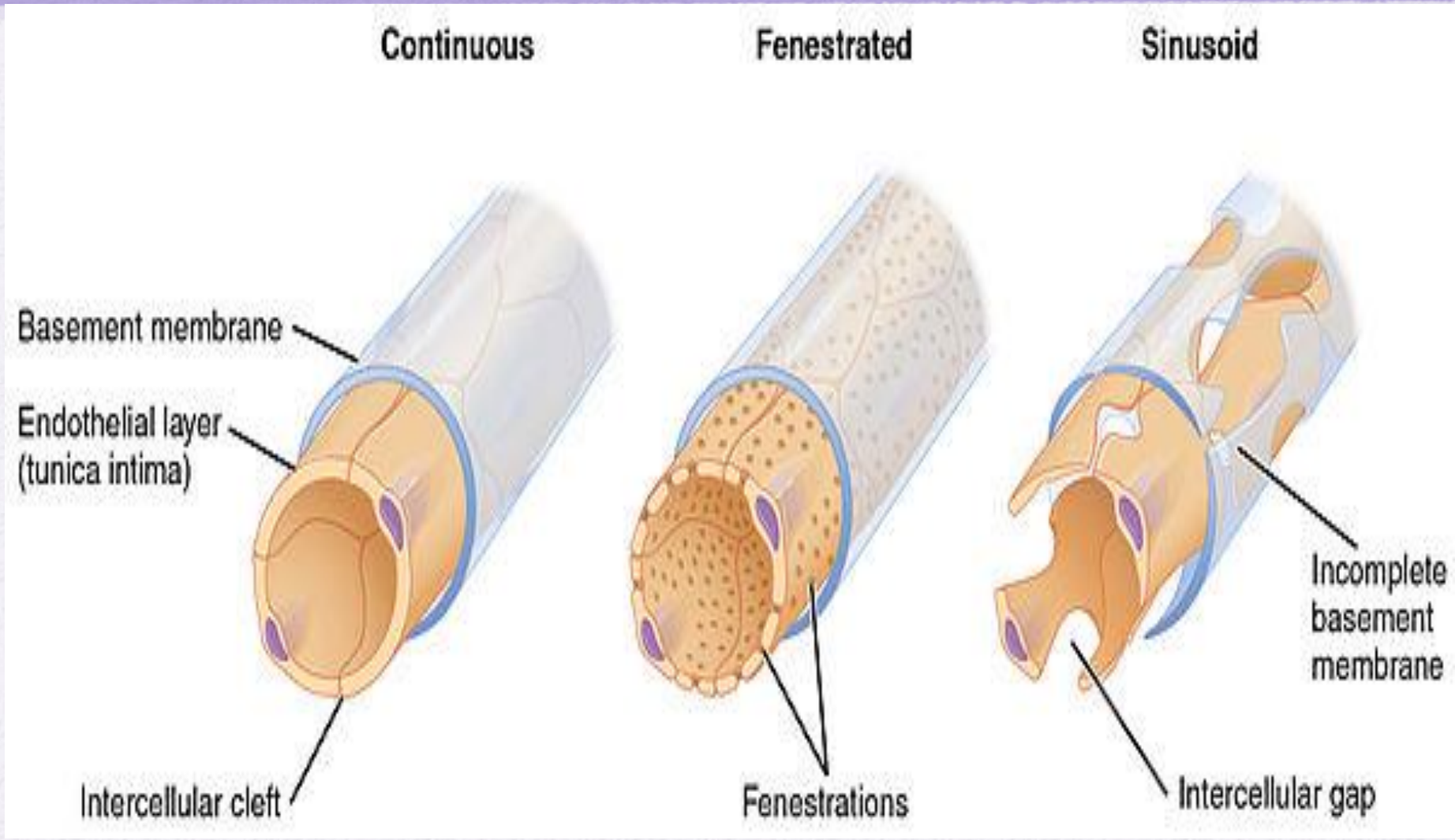
Types of Endothelial Cells

- Multifunctional tissue. 3 types
  (1)*Continuous capillaries* are the most common have no transcellular perforations & cells are joined by tight nonpermeable junctions.Eg muscle, fat, nervous tissue

- (2)*Fenestrated capillaries* have intracellular perforations called fenestrae and are more permeable than continuous capillaries.Eg renal glomeruli, intestinal villi, endocrine glands

- (3)Discontinuous capillaries have open spaces between endothelial cells are very permeable and may permit the passage of blood cells between them. Eg liver, spleen, bone marrow.

Types of Endothelial Cells



Endothelial Cells & Vascular smooth muscle cells

- (1)*Inflammation, septic shock:* with release of cytokines & bacterial products
  (2) *Atherosclerosis:* Hemodynamic stress & lipid products
  (3) *Diabetes:* advanced glycation end products(AGE's)
- Adhesion molecules; cytokines, pro-inflammatory factors,
- Vascular smooth muscle cells: Synthesis of ECM, collagen, elastin, proteoglycans, Prodn of cytokines(PGDF,FGF,NO,TGF-β) *Formation of neo-intima*(ec+smc)

ARTERIOSCLEROSIS

- Thickening & hardening of the arterial walls.

- Types:
  1)Senile arteriosclerosis *(Due to aging)* characterized by Fibroelastosis & Elastic Reduplication
  2)Hypertensive arteriolosclerosis : 3 forms
  (a)Hyaline arteriolosclerosis
  Physiological: Aging
  Pathological: (i) Benign Nephrosclerosis in hypertension (ii) Microangiopathy in diabetes, AGE's , hyperglycemia induced

ARTERIOSCLEROSIS

- *Pathogenesis:* Hemodynamic stress in HT & DM → Incr permeability of vasc endothelium → Leakage of plasma proteins & deposition in vessel wall → *Morphologic Change:* Eosinophilic hyaline appearance.

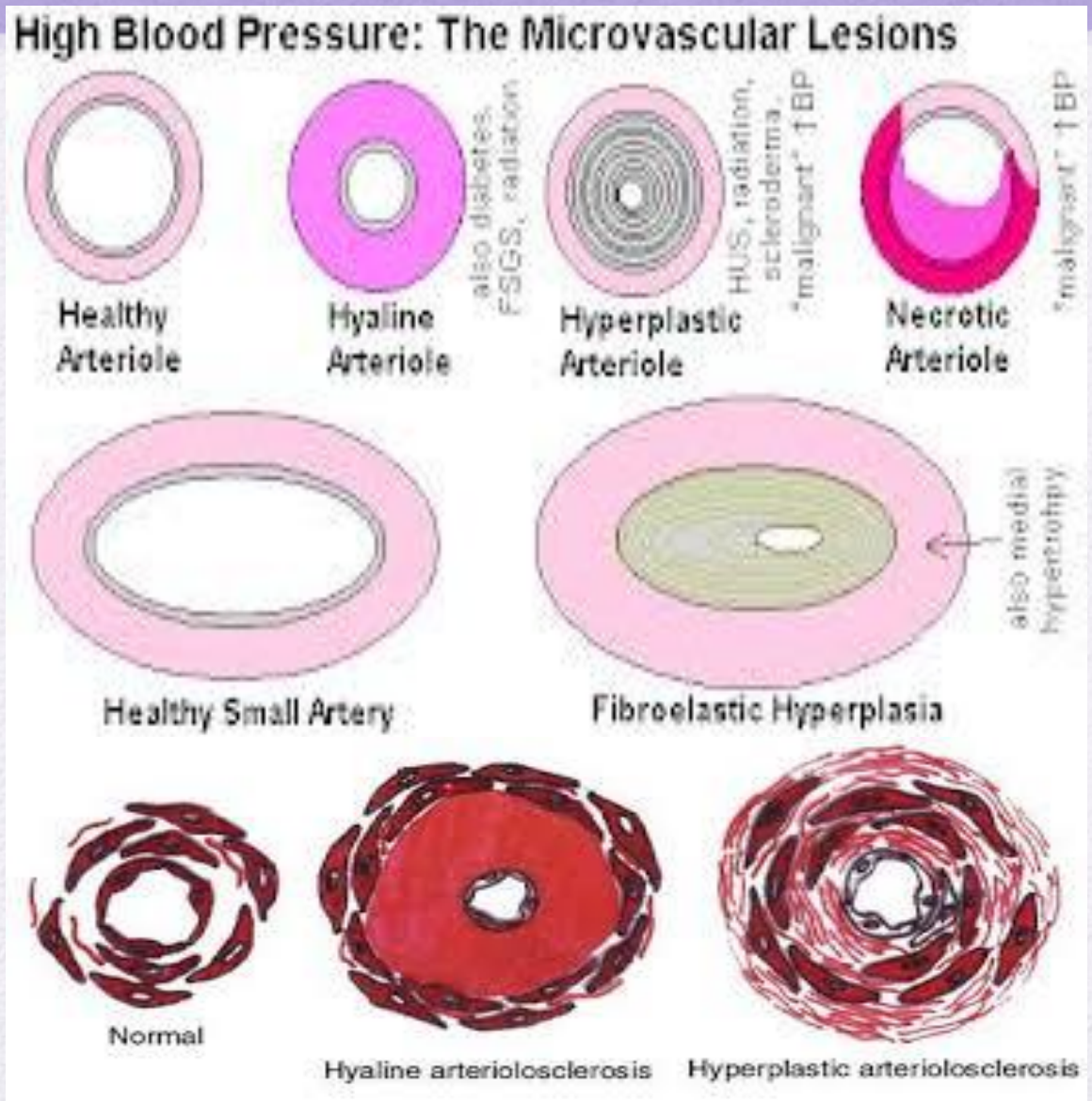
- *(b)Hyperplastic arteriolosclerosis* (i)Malignant hypertension (ii) Toxaemia of pregnancy (iii) Hemolytic-Uremia syndrome (iv) Scleroderma
  Pathogenesis: Systemic hypertension/hypoxia →Injury to endothelium → Hyperplastic intimal thickening with proliferation of smooth muscles & fibrosis.

ARTERIOSCLEROSIS

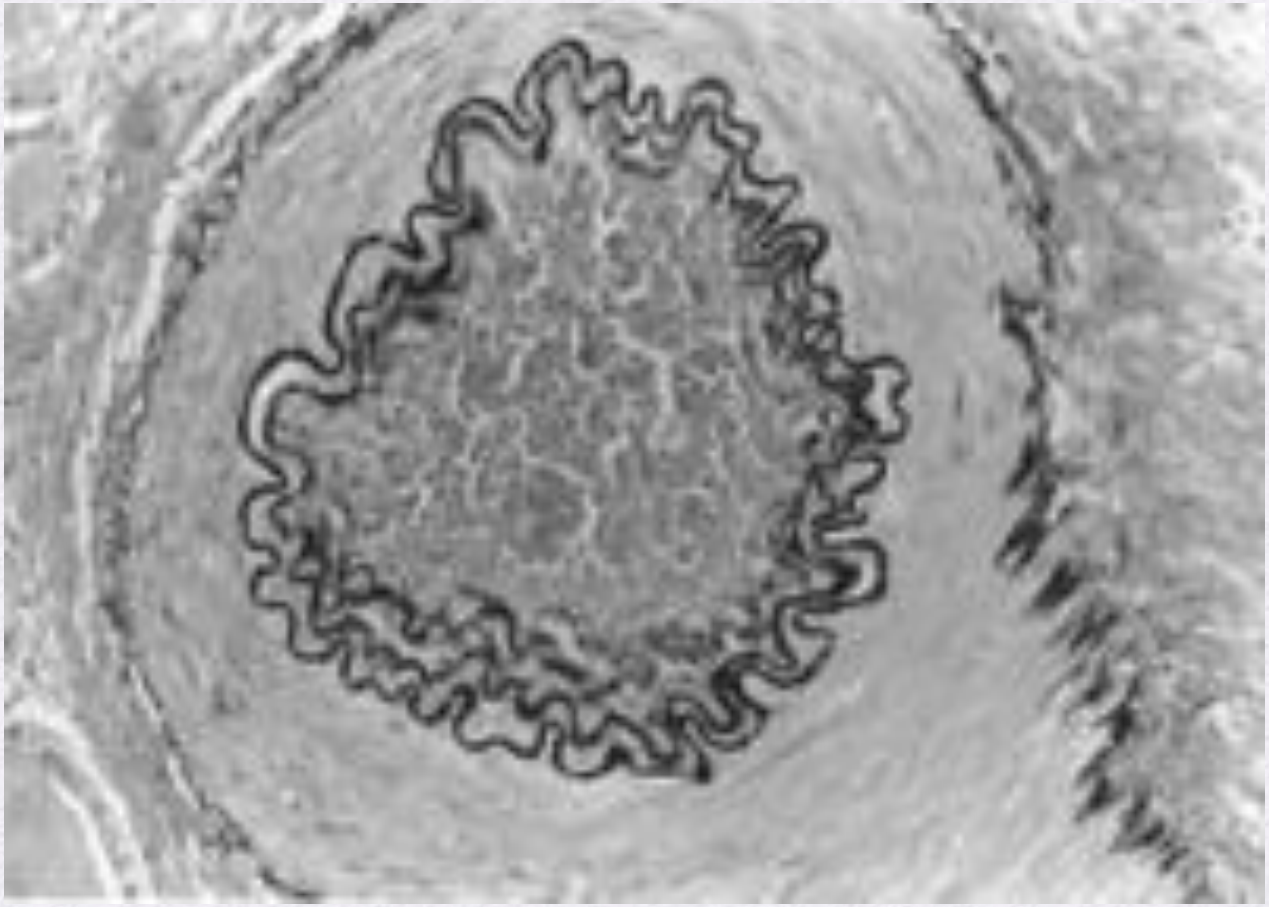
- *Morphology:* Intimal thickening of the interlobular renal arteries (3 types)
  (i) Onion skin appearance of hyperplastic intimal smooth ms cells
  (ii) Mucinous intimal thickening
  (iii) Fibrous intimal thickening with deposition of collagen & elastic fibres in the intima.

- *(c)Necrotizing arteriolitis:* Seen in Malignant hypertension in kidney, Necrosis may be superimposed on hyaline arteriosclerosis. *Morphology:* Fibrinoid necrosis of vessel wall, neutrophils in adventitia, edema, hemorrhages.

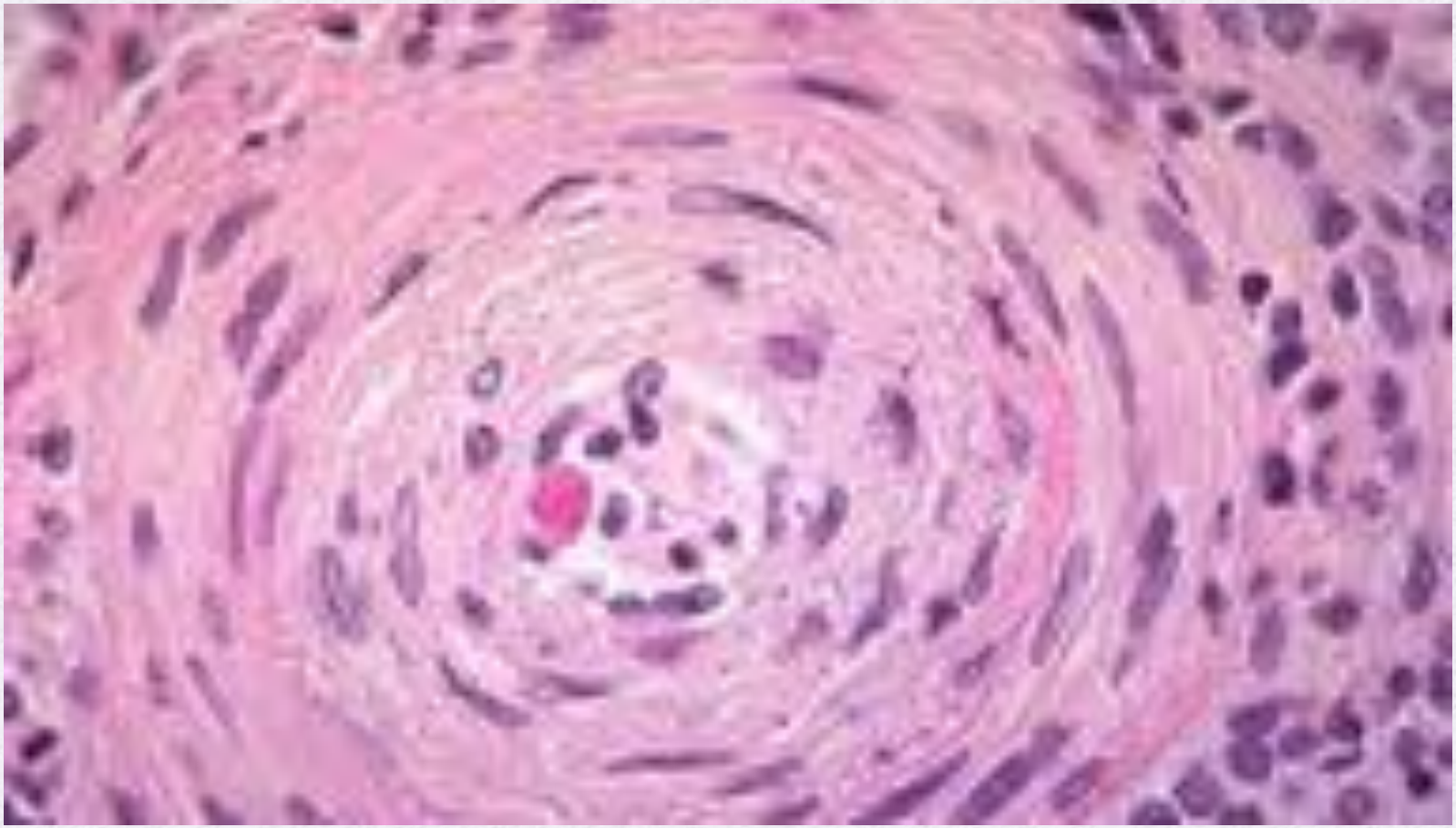
ARTERIOSCLEROSIS



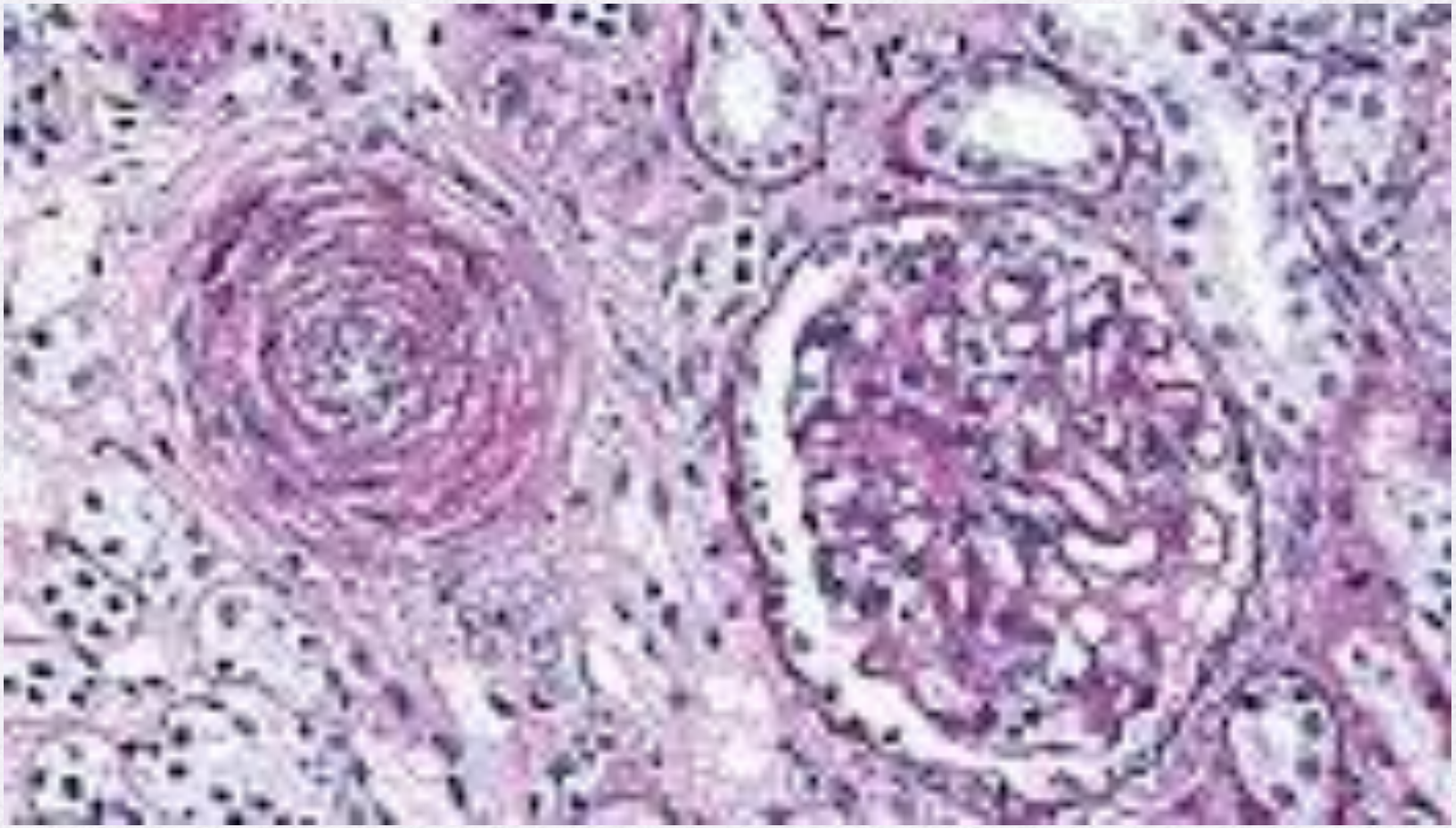
Reduplication of IEL



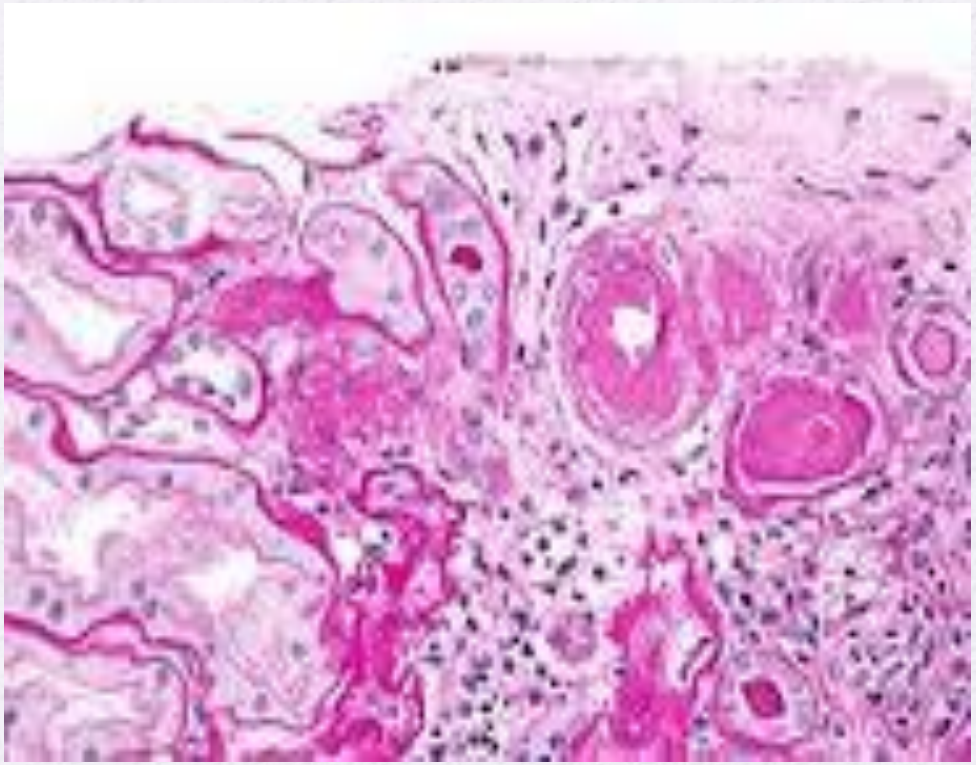
Hyperplastic Arteriolosclerosis

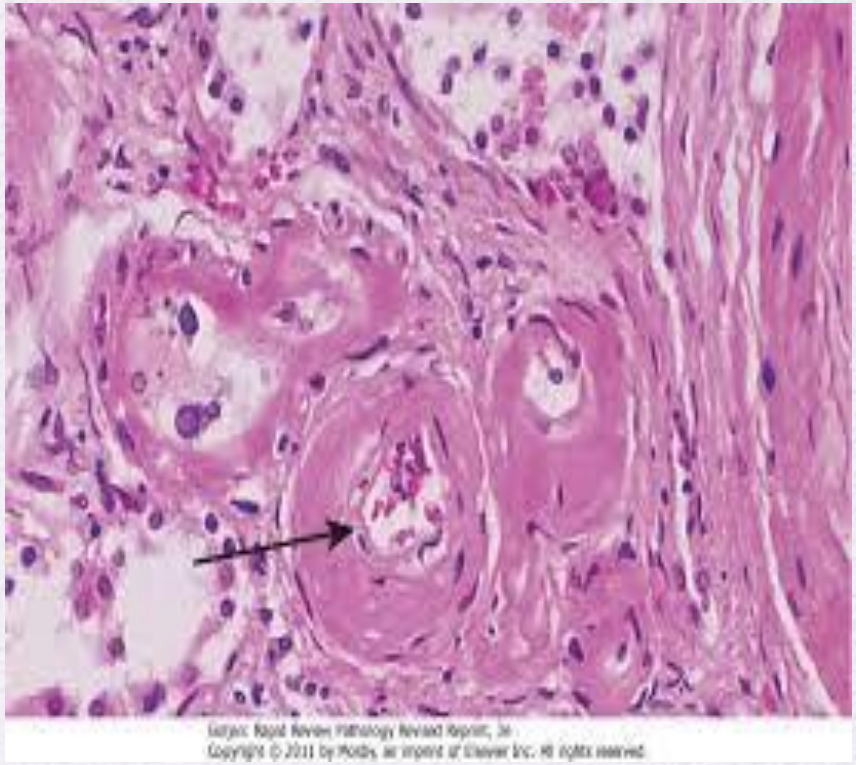


Hyperplastic Arteriolosclerosis



Renal Artery Hyalinosis



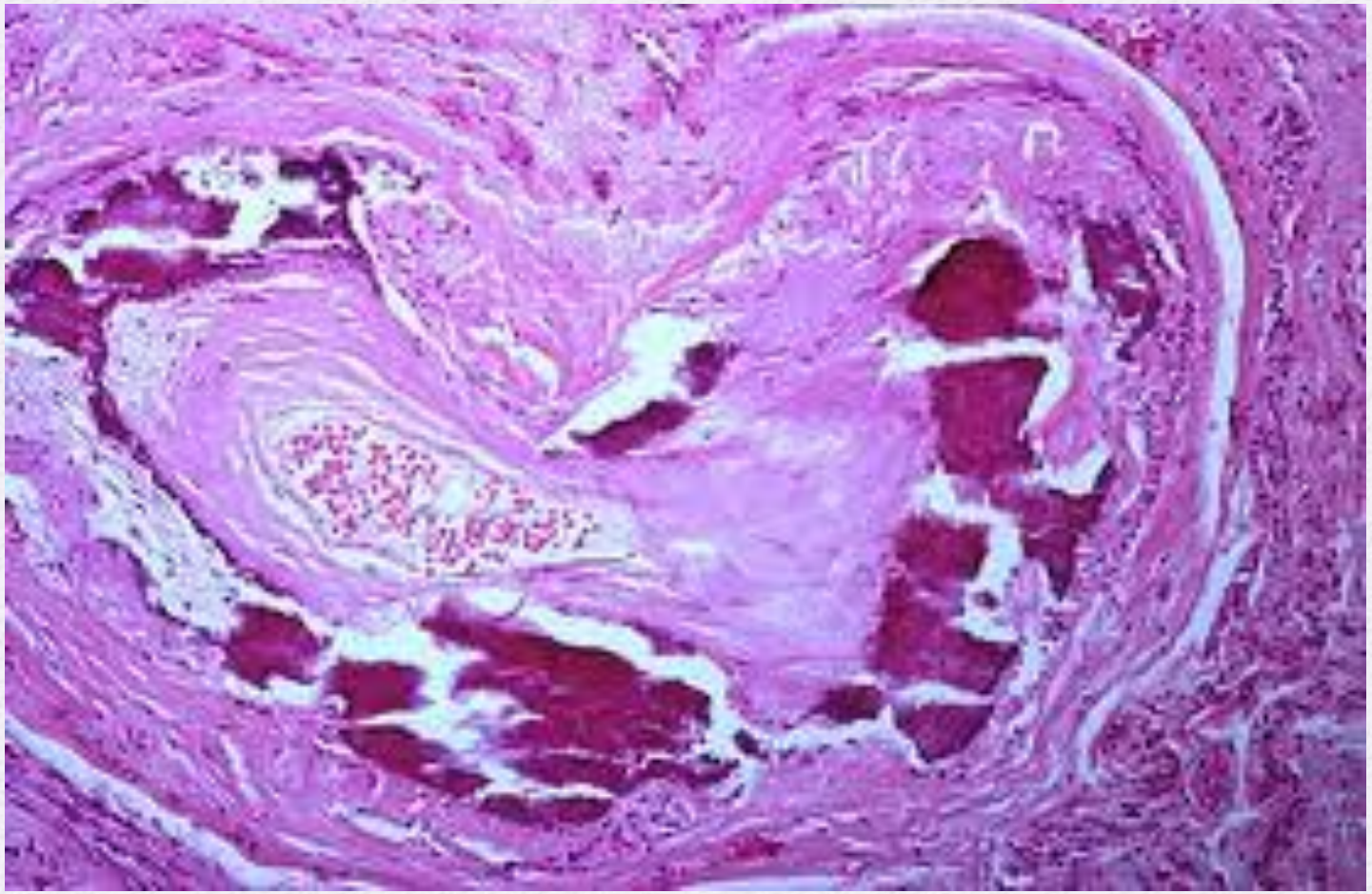


ARTERIOSCLEROSIS

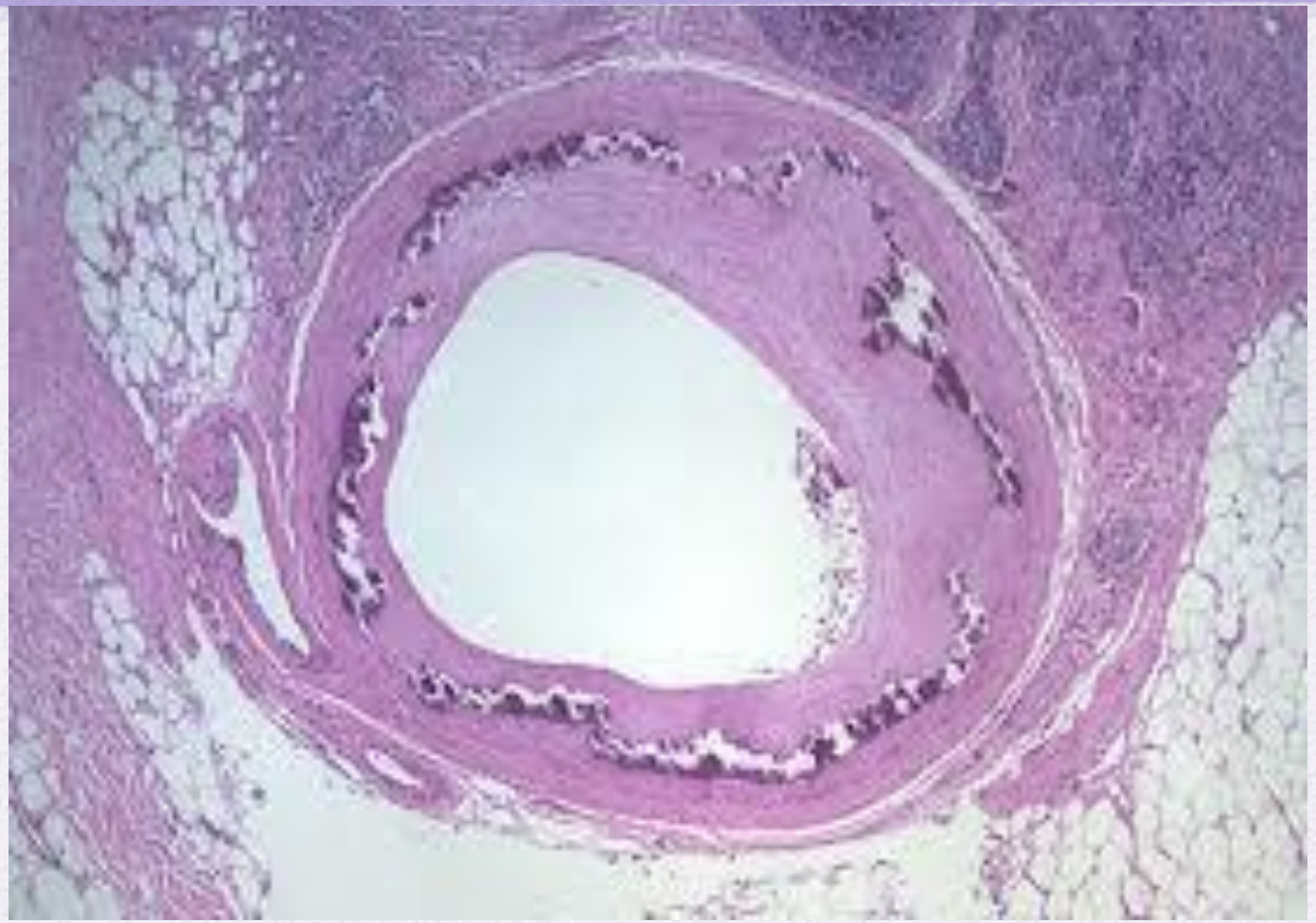
- **3)Monkeberg's medial calcific sclerosis**
  Age related degenerative process.

- *Morphology:* Calcification of media of the muscular arteries of the arteries & genital tract (dystrophic)
  Intima & media are usually spared
  No associated inflammatory reaction

Monkeberg's Medial Calcific Sclerosis



Monkeberg's Medial Calcific Sclerosis



ATHEROSCLEROSIS

- A specific type of arteriosclerosis affecting the intima of large & medium sized muscular arteries characterized by fibrofatty plaques or '*atheromas*'
- **Large elastic arteries:** Aorta, Carotid, iliac
  Medium sized arteries: coronary, popliteal;
- Atheroma➔Ischemia➔Angina/Myocardial infarction/Cerebral infarcts/Strokes.
- Can also lead to Peripheral Vascular Disease, Aneurysmal dilatation(weakened arterial wall) chronic ischaemic heart disease, ischaemic encephalopathy,mesentric artery occlusion

Risk Factors: ATHEROSCLEROSIS

- **Framingham Heart Study**: Prospective study in pt populations

- **Major Risk Factors: (I) Modifiable:**
  (1) Dyslipidemia (2)Hypertension (3) Diabetes mellitus (4)Smoking
  (II) Constitutional:
  (1) Age (2) Sex (3) Genetic factors (4) Familial factors

- **(II) Emerging Risk Factors:** uncertain role
  (1)Lipoprotein(a) (2)Metabolic syndrome(3)Prothrombotic factors (4)Hyperhomocystinemia (5)Infections, eg *C. pneumoniae*, *Herpesvirus*, *CMV* (6)High CRP(7) Obesity/Stress Type 'A' personality/lack of exercise.

Hyperlipidemia

- Abnormalities in plasma lipoproteins/hypercholesterolemia is rel to Atherosclerosis & IHD
  (1)AS plaques contain cholesterol & cholesterol esters derived from lipoproteins.
  (2)Diets rich in cholesterol can induce lesions of atherosclerosis (experimental animals)
  (3)Hypercholesterolemia in DM, myxoedema, nephrotic syndrome, von Gierkes disease→Increased risk of atherosclerosis & IHD
  (4)Dietary regulation & cholesterol lowering drugs reduce risk of IHD.

Hyperlipidemia

- Hypercholesterolemia – LDL cholesterol
  Total Cholesterol : Lipoproteins in serum –i.e. Chylomicrons/ VLDL/ LDL/HDL. Lipids are attached to apoproteins(carrier proteins)
- S-Cholesterol : 140 to 200 mg/dl 'Ideal levels'
  Serum levels > 260 mg/dl , 3 times higher risk of developing IHD.
- Diet : Prefer Poly unsaturated fats & Omega 3 fatty acids.
  Avoid Saturated fats & Trans fats
  Lowering of LDL: Statins (inhibit HMG-CoA reductase)

Hypertension

- Induction of oxidative stress due to ↑sed prodn of free radicals. (Leucocyte adhesion, macrophage accumulation, smooth muscle migration & proliferation & intimal thickening)
- Mechanical injury to the arterial wall due to increased blood pressure. Important cause of LVH
- Systolic Blood pressure > 160 mmHg
- Diastolic Blood Pressure > 95 mmHg

} 5 times higher risk

Smoking

- **SMOKING:** impacts all phases of atherosclerosis from endothelial dysfunction to acute clinical events, esp thrombotic.
  Increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol.

- Increased risk of atherosclerotic IHD & Sudden Cardiac Death.(30%-Passive smokers 80% -Active smokers)
  Causes: (1) reduced levels of HDL
  (2)deranged coagulation system
  (3)Accum of CO in blood/CarboxyHb➔Hypoxia➔ endothelial dysfunction➔ AS

Diabetes mellitus

- Glycation and oxidation of lipids and other proteins contribute to the development of AS in individuals with diabetes via the formation of advanced glycation end products (AGE's)
- 'Atherogenic dyslipidemiaemia'→ Increased risk of AS
- Increased Risk of MI, Stroke, Gangrene of lower limbs.
- Poor Glycemic control in DM associated with microvascular disease.
  Improvement in glycemic control→ Slows progression of AS in diabetes patients.

Emerging Risk Factors

- **Inflammation :** linked to plaque formation & rupture. Long standing inflamm assoc with ↑ ed risk of CAD *Helicobacter pylori, Chlamydia pneumoniae, Mycoplasma pneumoniae.* Periodontal pathogens.
- *highly sensitive CRP*
  Lipoprotein-Phospholipase A2

  ] Predict ↑sed risk
- predict the risk of MI, stroke, peripheral arterial disease & sudden cardiac death

Hyperhomocysteinemia

- Characterized by increased levels of amino acid Homocysteine in urine & elevated levels in blood.
- Mild hyperhomocysteinemia is an independent risk factor for Atherosclerosis.
- Hyperhomocystinemia associated with CAD, PVD, stroke, venous thrombosis

Metabolic Syndrome

- **Criteria:**
- 1. Abdominal obesity: BMI >30 kg/m2 and/or waist:hip ratio >0.9 in men, >0.85 in women
- 2. Hypertension: ≥140/90 mm of Hg or on antihypertensive treatment
- 3. Elevated triglycerides (≥150 mg/dl) and/or reduced HDL-C (<39 mg/dl for both men and women)
- 4. Elevated plasma glucose: impaired fasting glucose (IFG) or IGT, but no diabetes

Lipoprotein(a) Lp(a)

- Lipoprotein subclass which is a risk factor for atherosclerotic diseases such as CAD, stroke.
- High Lp(a) predicts risk of early AS independently of other cardiac risk factors, including LDL.
- Lp(a) accumulates in the vessel wall ➔ inhibits binding of Plasminogen ➔ increases clotting& promotes proliferation of smooth muscle cells.
- Lp(a) directly contribute to atherosclerotic damage by increasing plaque size, inflammation and smooth muscle cell growth.

PATHOGENESIS

- 'Response to Injury Hypotheses' : Endothelial injury leading to chronic inflammation & healing response.
  (1) Endothelial injury - ↑sed vascular permeability, leukocyte adhesion, thrombosis
  (2) Accumulation of LDL in the vessel wall
  (3) Monocyte adhere to endothelium→Migrate into intima→Transform into macrophages & foam cells.
  (4) Platelet adhesion
  (5)Release of cytokines→Smooth muscle recruitment
  (6) Smooth muscle proliferation &prodn of extracellular matrix (6) Accum of lipid-extracellularly& within macrophages & sm cells.

Pathogenesis (contd)

- Endothelial injury– initiating factor :
  Injury(hemodynamic forces, chemical, irradiation, immune complex deposition) Dysfunctional endothelium - ↑sed permeability, adhesion & altered gene expression.
- Causes: hypertension, hyperlipidemia, toxins from cigarette smoke, homocysteine, inflammatory cytokines
- Hemodynamic disturbances- plaques seen at branch points, ostia, posterior wall of abdominal aorta ch by disturbed flow patterns,

Pathogenesis (contd)

- **Lipids:** Increased LDL, Decreased HDL, Increased Lipoprotein a.
- Oxygen free radicals→oxidised LDL→Ingestion by macrophages→Formation of foam cells.
- Oxidised LDL→Release of cytokines→Further accumulation of monocytes(transform into macrophages) & T lymphocytes.

MORPHOLOGY

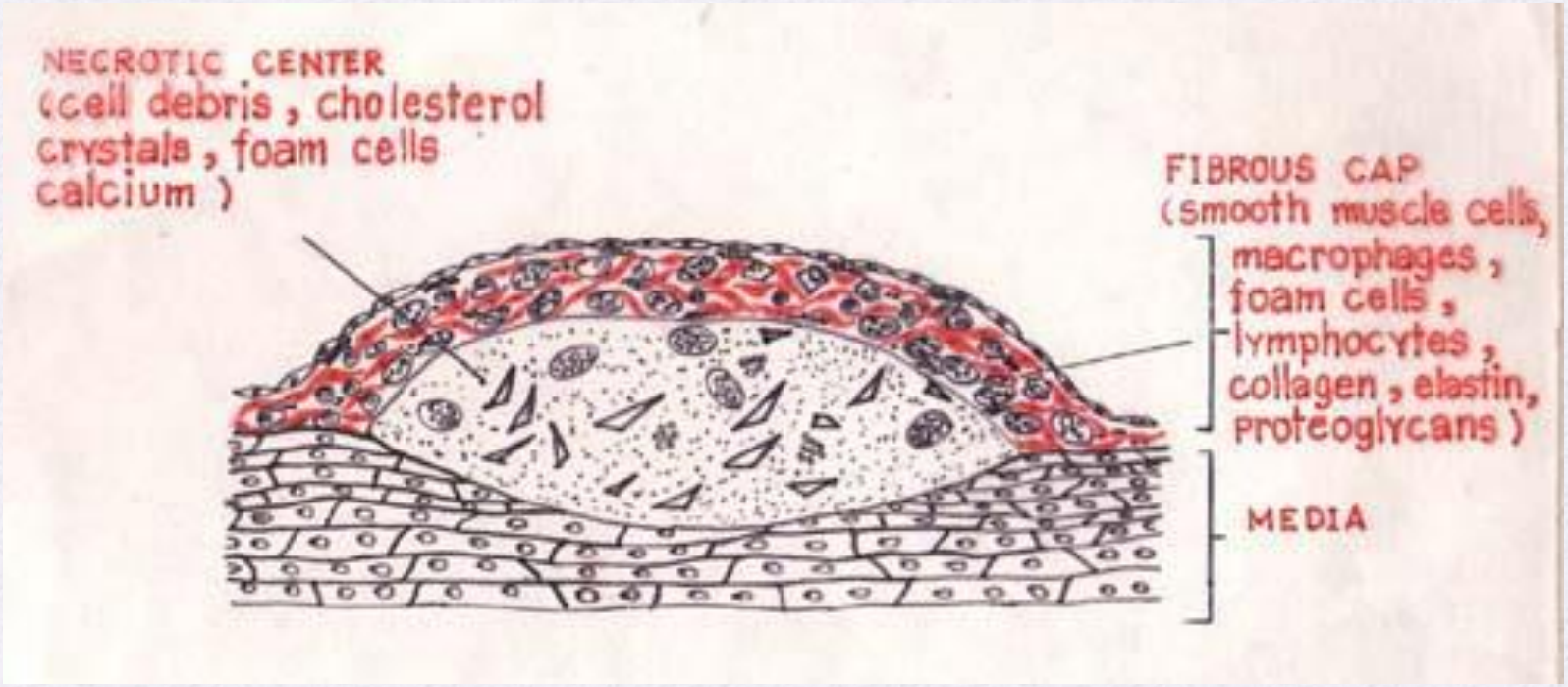
- **EARLY LESIONS :**
  (1) Fatty streaks & dots – Aorta, 1st year of life.
  All races, different environments, both sexes.
  Yellow streaks, 1 cm length-lipid filled macrophages.
  Precursor of AS plaque ?
  Coronary fatty streaks- at adolescence
  (2) Gelatinous lesions-Round to oval greyish elevations about 1 cm dia- Increased Ground substance in intima.

MORPHOLOGY

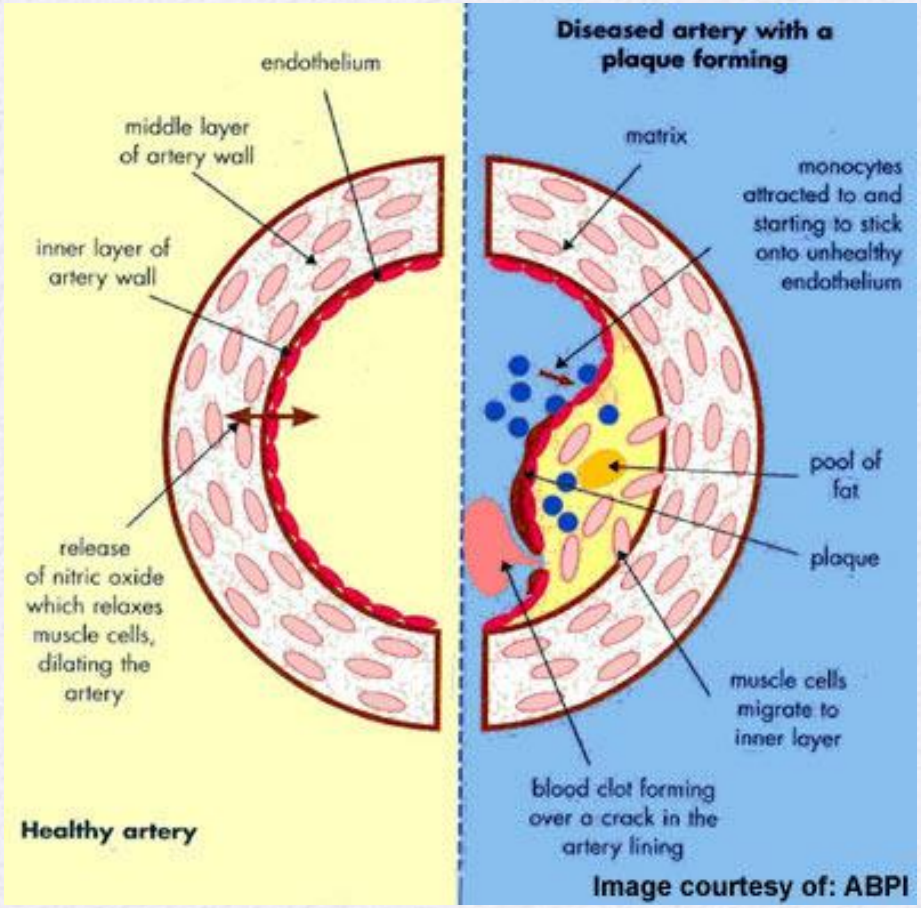
- **ATHEROSCLEROTIC PLAQUE:**
  (1) INTIMAL THICKENING (2) LIPID ACCUMULATION

- Atherosclerotic plaques composed of:
  (1) Smooth muscle cells, Macrophages, T lymphocytes.
  (2) Extracellular Matrix (ECM)which include collagen, elastic fibres & proteoglycans.
  (3) Intracellular & Extra cellular lipids.

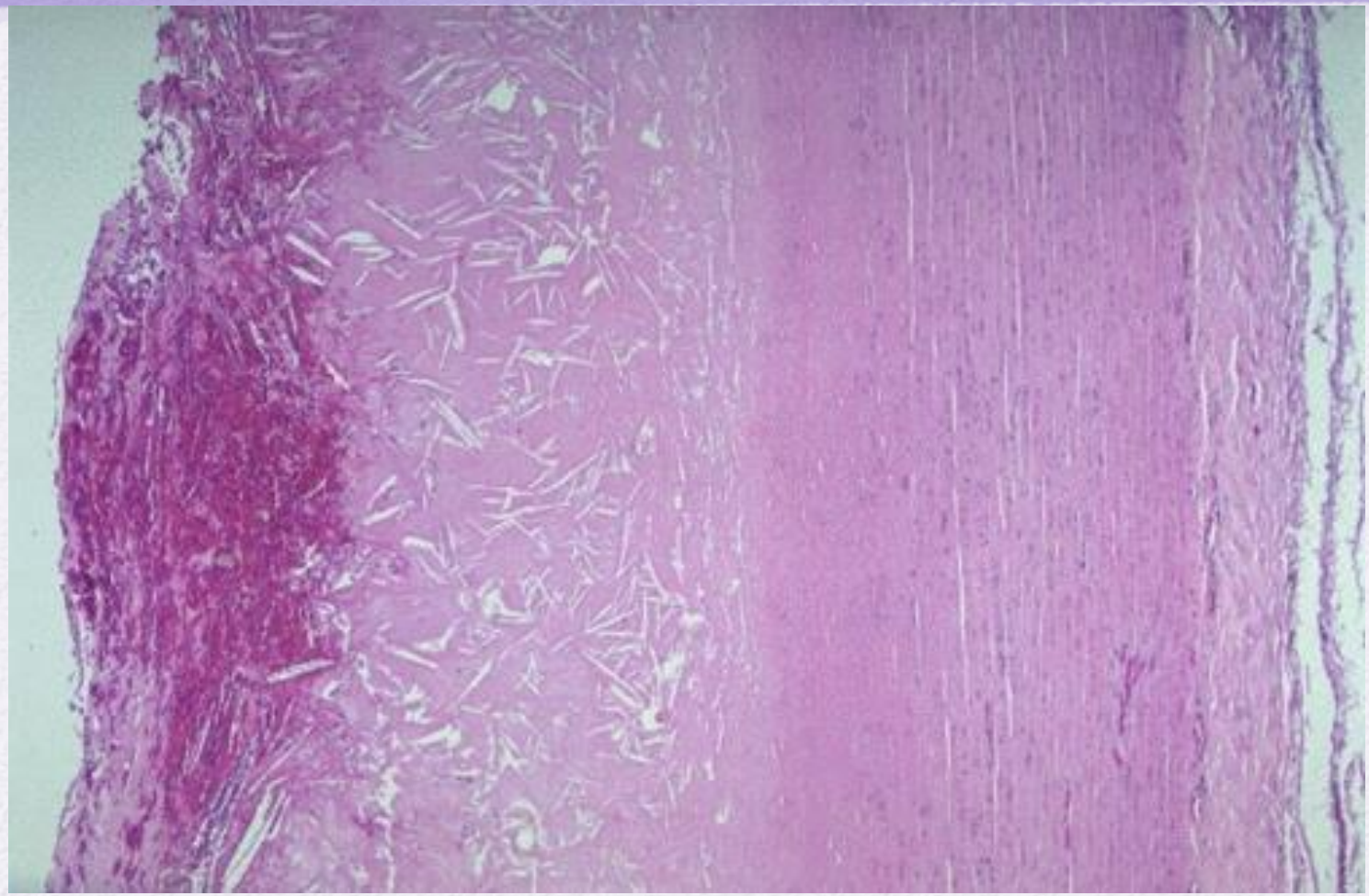
Atheroma: Line Diagram



Atheroma: Line Diagram



Atheromatous plaque with cholesterol clefts



MORPHOLOGY

- **ATHEROSCLEROTIC PLAQUE:**
  (1) Superficial fibrous cap-Smooth muscle cells & collagen
  (2) Shoulder is the cellular area with Smooth muscle cells, Macrophages, T lymphocytes.
  (3) In the centre is the Necrotic core- Lipids, debris from dead cells, lipid laden macrophages & sm cells.
  (3) Intracellular & Extra cellular lipids.
  (4)Neo-Vascularization at the periphery

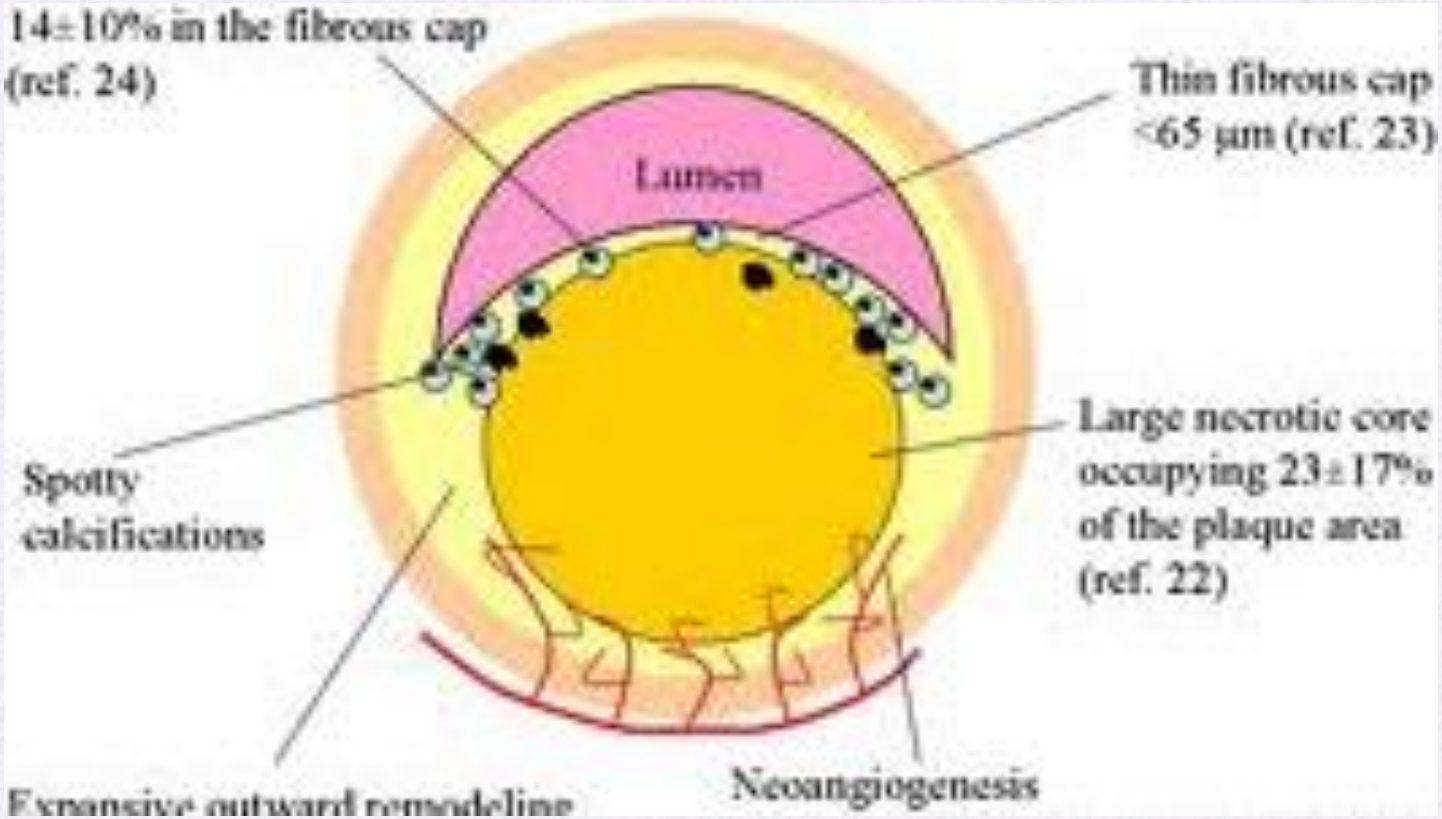
MORPHOLOGY

- **ATHEROSCLEROTIC PLAQUE (COMPLICATED):**
  (1) Calcification in the atheroma
  (2) Ulceration/Erosion of the fibrous cap➔Thrombosis
  (3) Haemorrhage into a plaque➔Expanding hematoma➔Plaque rupture
  (4)Atheroembolism: Discharge of atherosclerotic debris into the bloodstream, producing microemboli.(5)Aneurysm formation➔Ischemic atrophy of the underlying media with loss of elastic tissue➔Weakness & aneurysmal dilatation➔chances of rupture.

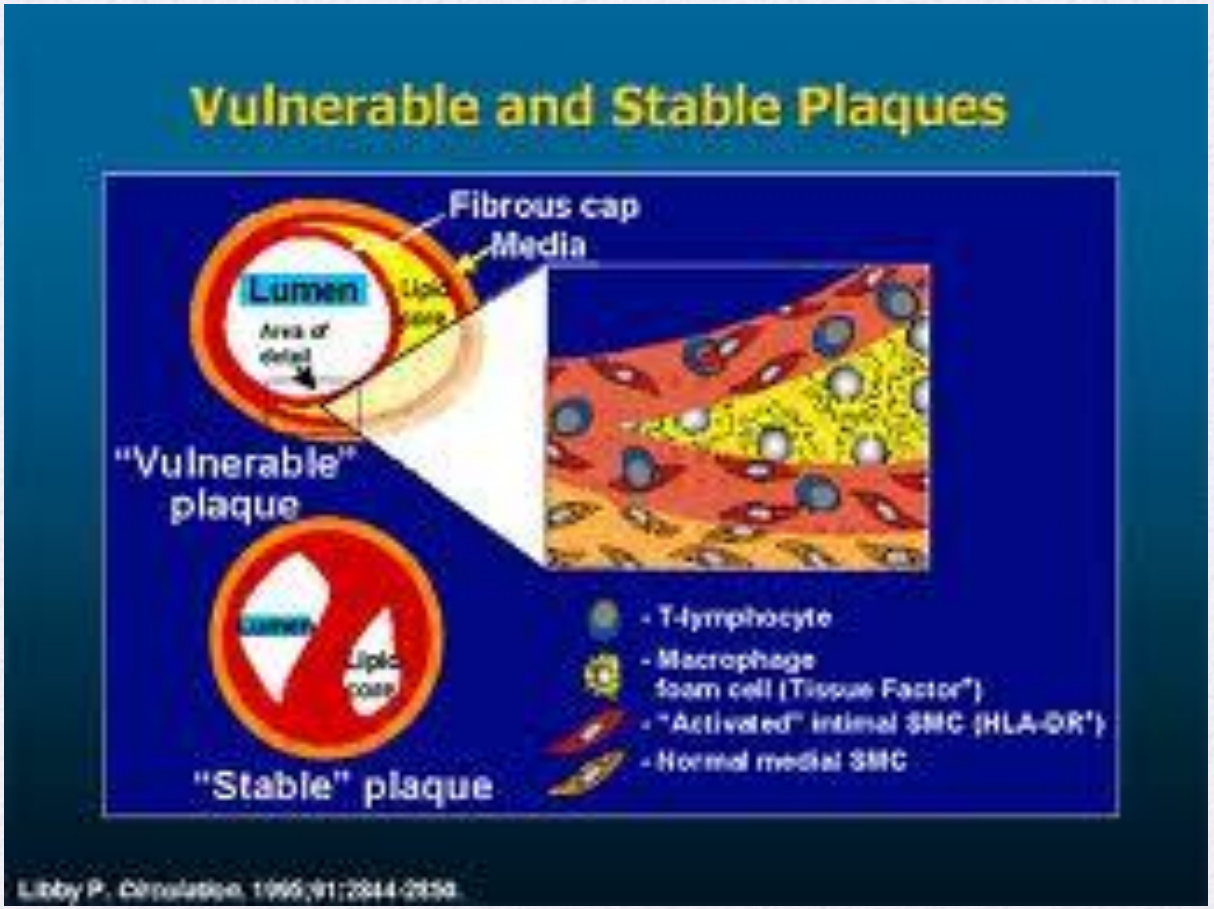
Complications/Consequences of AS

- Clin: Myocardial infarction, Cerebral infarction, aortic aneurysm, Peripheral vascular disease
- Plaque rupture→Emboli of AS debris→distal vessel obstruction→Tissue perfusion affected →Infarction. Distal Vessel obstruction can also lead to Acute vascular thrombosis.
- Weakening of vessel wall→Aneurysm formation→Secondary rupture & Thrombosis
- Acute Plaque change/Thrombosis/AS stenosis/Vasoconstriction

Vulnerable Plaque



Vulnerable/Stable Plaque



Acute Plaque Change

- Fissure/Rupture: Exposing of highly thrombogenic plaque constituents
- Erosion/Ulceration:
- Hemorhage into the atheroma
- Abrupt Changes in plaque: **Intrinsic factors** (Thin fibrous cap, ↑sed foamcells & lipid, ↓sed sm ms cells. **Extrinsic factors** (hypertension, adrenergic stimulation, *"Vulnerable plaques"* , ↑sed secretion of NO, ↓sed secretion of endothelin.)

Atherosclerotic stenosis

- AS stenosis: Early stages – Outward remodelling of media➔ Preserve luminal diameter.
  Late stages: Chronic occlusion *"Critical stenosis"*

- Clinical pres: Angina. Acute Plaque rupture ; Chronic decreased arterial perfusion(chronic IHD, bowel ischemia, intermittent claudication)