PATHOLOGY OF CARDIOVASCULAR SYSTEM

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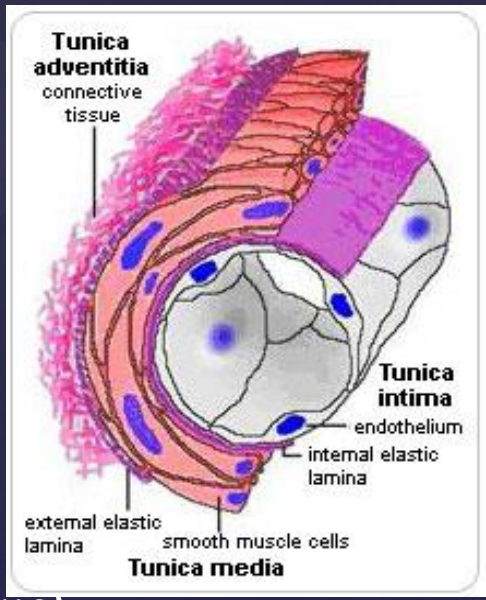
Diseases of Blood Vessels

Function of endothelial cells lined blood vessels

1. *Maintenance of Permeability Barrier*
2. *Elaboration of Anticoagulant, Antithrombotic, Fibrinolytic*
3. *Regulators*
    - Prostacyclin
    - Thrombomodulin
    - Heparin-like molecules
    - Plasminogen activator
4. *Elaboration of Prothrombotic Molecules*
    - Von Willebrand factor
    - Tissue factor
    - Plasminogen activator inhibitor
5. *Extracellular Matrix Production (collagen, proteoglycans)*
6. *Modulation of Blood Flow and Vascular Reactivity*
    - Vasconstrictors: endothelin, ACE
    - Vasodilators: NO, prostacyclin



7. Regulation of Inflammation and Immunity

- IL-1, IL-6, chemokines
- Adhesion molecules: VCAM-1, ICAM, E-selectin P-selectin
- Histocompatibility antigens

8. Regulation of Cell Growth

- Growth stimulators: PDGF, CSF, FGF
- Growth inhibitors: heparin, TGF-β

9. Oxidation of LDL

Endothelial cells activated cytokines & bacterial prod. → Inflammation and septic shock; hemodynamic stresses and lipid products, critical to the pathogenesis of atherosclerosis; advanced glycosylation end products (important in diabetes), as well as viruses, complement components, and hypoxia.

Vascular smooth muscle cells vasoconstriction and dilation → response to normal or pharmacologic stimuli.
They also synthesize collagen, elastin, and proteoglycans; and elaborate growth factors and cytokines. They migrate to the intima and proliferate following vascular injury.

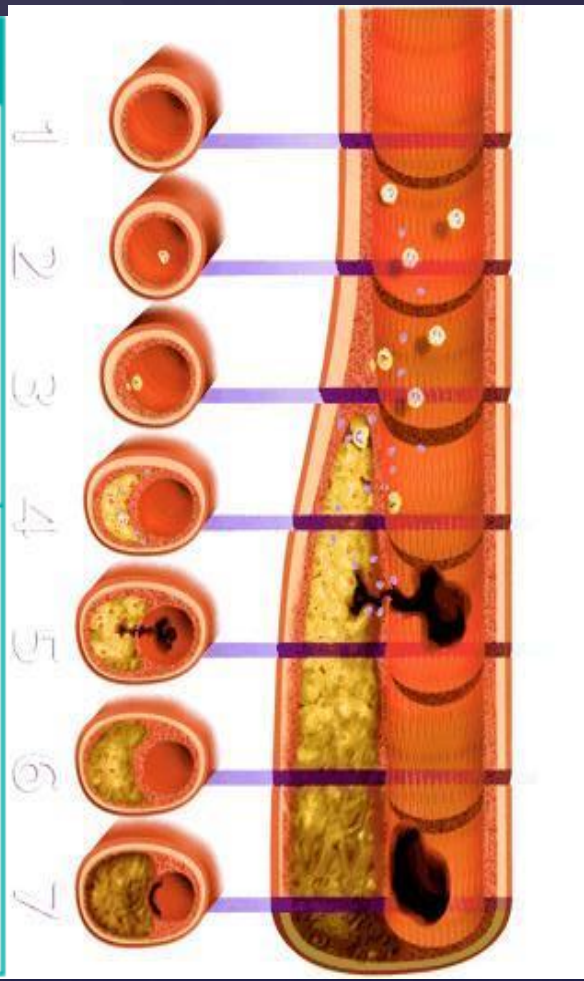
1. Atherosclerosis

Intimal lesions called atheromas, or atheromatous or fibrofatty plaques, which protrude into and obstruct vascular lumens.

It is the cause of ischæmic heart disease.

The American Heart Association classification divides atherosclerotic lesions into **six** types:

Nomenclature and main histology	Sequences in progression	Main growth mechanism	Earliest onset	Clinical correlation
Type I (initial) lesion Isolated macrophage foam cells	I	Growth mainly by lipid accumulation	From first decade	Clinically silent
Type II (fatty streak) lesion Mainly intracellular lipid accumulation	II			
Type III (intermediate) lesion Type II changes and small extracellular lipid pools	III		From third decade	
Type IV (atheroma) lesion Type II changes and core of extracellular lipid	IV			Clinically silent or overt
Type V (fibroatheroma) lesion Lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific, or mainly fibrotic	V	Accelerated smooth muscle and collagen increase	From fourth decade	
Type VI (complicated) lesion Surface defect, hematoma-hemorrhage, thrombus	VI	Thrombosis, hematoma		



- Fatty streaks are the earliest lesion of atherosclerosis, composed of subendothelial lipid-filled foamy cells, with few T lymphocytes and extracellular lipid, appear in the aorta in all children above the age of 10.
- Some fatty streaks may progress to atheromatous plaques, developing primarily in elastic arteries (e.g., aorta, carotid, and iliac arteries) and large and medium-sized muscular arteries (e.g., coronary and popliteal arteries), resulting in partial or complete obstruction.
- In small arteries plaques can undergo disruption and precipitate thrombi that further obstruct blood flow.

Atherosclerotic plaques have three principal components:

1. cells, including SMCs, macrophages, and other leukocytes;
2. ECM, including collagen, elastic fibers, and proteoglycans;
3. intracellular and extracellular lipid (cholesterol and cholesterol esters).

Complications:

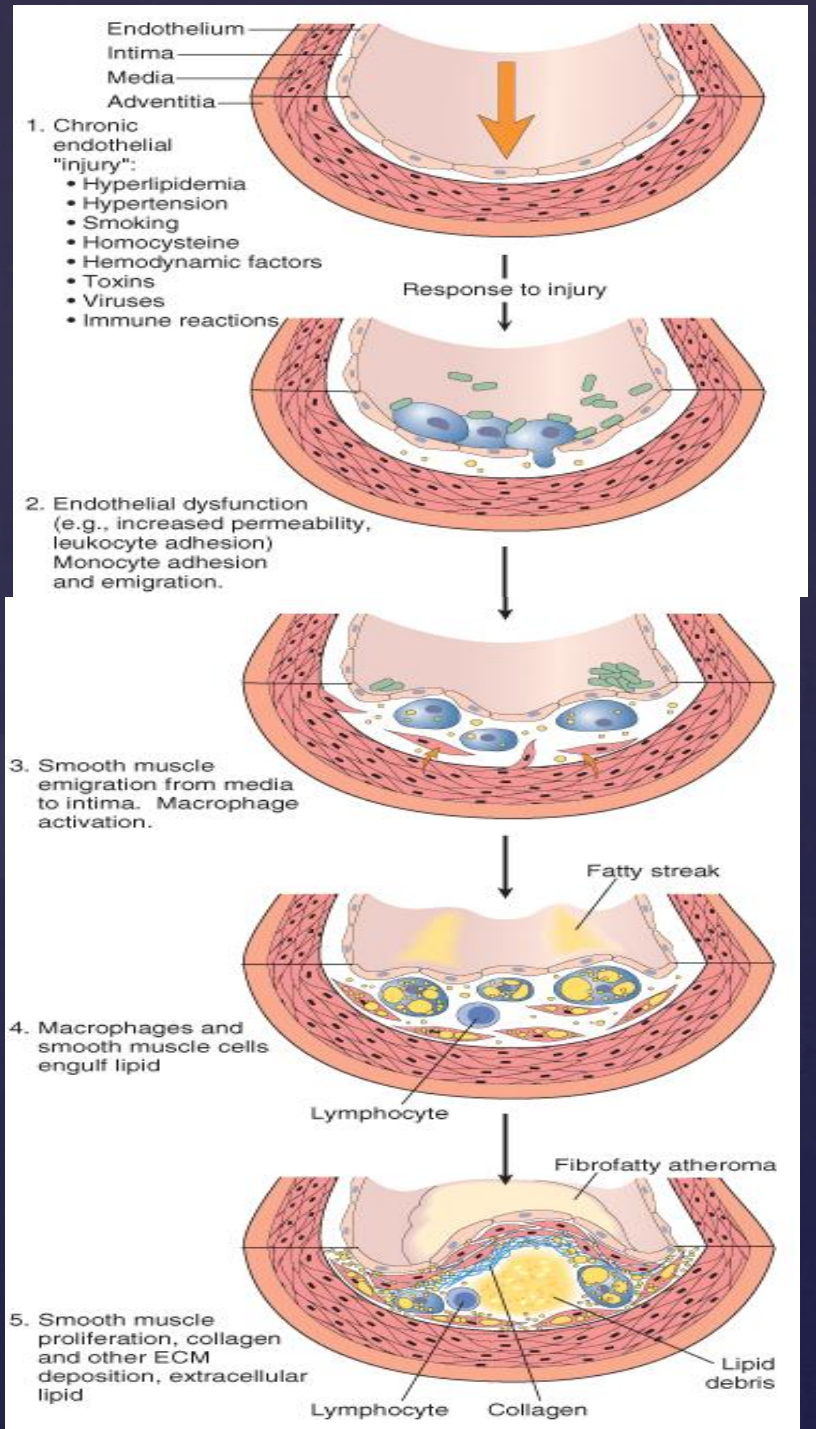
- Rupture, ulceration and erosion.
- Hæmorrhage into the plaque.
- Thromosis.
- Aneurysmal dilatation.

Risk factors of IHD:

Major	Minor
Non-modifiable	
Increasing age Male gender Family history Genetic abnormalities	Obesity Physical inactivity Stress ("type A" personality) Postmenopausal estrogen deficiency High carbohydrate intake
Potentially Controllable	
Hyperlipidemia (cholesterol) Hypertension Cigarette smoking Diabetes	Alcohol Lipoprotein Lp(a) Hardened (trans)unsaturated fat intake Chlamydia pneumoniæ

Pathogenesis

- Chronic endothelial cell injury.
- Accumulation of lipoproteins mainly LDL.
- Oxidation of lipoproteins.
- Migration of monocytes to the intima, phagocytosing lipids (foam cells).
- Adhesion of platelets.
- Smooth muscle cell migration to the intima and proliferation.
- Enhanced accumulation of lipids



2. Hypertension:

One of the most important risk factors for both **coronary artery disease and cerebrovascular accidents**;
it can lead to **cardiac hypertrophy and, potentially, heart failure (hypertensive heart disease), aortic dissection, and renal failure**.

Pathogenesis

multifactorial depending on genetic and environmental causes, but the main cause of hypertension remains unknown in most of the cases. Hypertension is defined as a sustained diastolic pressure greater than 90 mm Hg or a sustained systolic pressure in excess of 140 mm Hg. It is estimated that 25% of the population are hypertensive.

Types and Causes

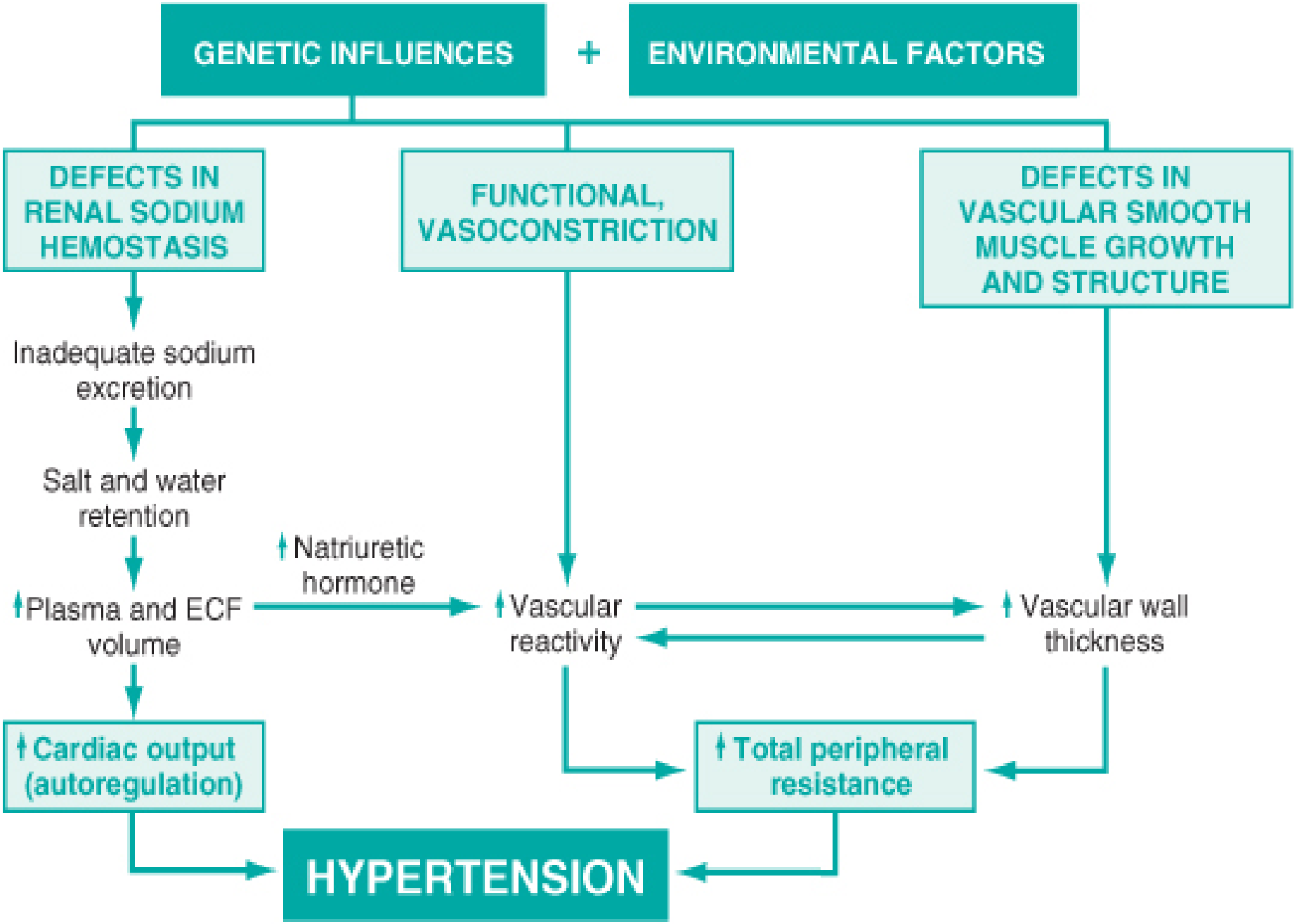
I. Essential Hypertension.
II. Secondary Hypertension:
1. Renal
- Acute glomerulonephritis
- Chronic renal disease
- Polycystic disease
- Renal artery stenosis
- Renal artery fibromuscular dysplasia
- Renal vasculitis
- Renin-producing tumors

2. Endocrine
   - Adrenocortical hyperfunction (Cushing syndrome, 1° aldosteronism, congenital adrenal hyperplasia, licorice ingestion)
   - Exogenous hormones (glucocorticoids, estrogen [pregnancy & oral contraceptives], sympathomimetics and tyramine-containing foods, monoamine oxidase inhibitors)
   - Pheochromocytoma
   - Acromegaly
   - Hyperthyroidism (thyrotoxicosis)
   - Hypothyroidism (myxœdema)
3. Pregnancy-induced
4. Cardiovascular
   - Coarctation of aorta
   - Polyarteritis nodosa (or other vasculitis)
   - ↑ intravascular volume & ↑ COP
   - Rigidity of the aorta

5. Neurologic
   - Psychogenic
   - Increased intracranial pressure
6. Sleep apnea
7. Acute stress, including surgery

The kidneys play an important role in regulation of BP:

- Renin-angiotensin system: Ang II raises BP by increasing both peripheral resistance and blood volume (stimulation of aldosterone secretion, increase in distal tubular reabsorption of sodium).
- Production of PG & NO, resulting in reduction of BP.
- Conservation of blood volume by reabsorption of sodium.
- Natriuretic peptide inhibit sodium reabsorption and rennin-angiotensin system.
- Impairment of renal excretory function will result in increased renal blood flow by increasing BP to compensate for the reduced blood volume.


GENETIC INFLUENCES
+
ENVIRONMENTAL FACTORS
DEFECTS IN RENAL SODIUM HEMOSTASIS
FUNCTIONAL, VASOCONSTRICTION
DEFECTS IN VASCULAR SMOOTH MUSCLE GROWTH AND STRUCTURE
Inadequate sodium excretion
Salt and water retention
↑Plasma and ECF volume
↑Natriuretic hormone
↑Vascular reactivity
↑Vascular wall thickness
↑Cardiac output (autoregulation)
↑Total peripheral resistance
HYPERTENSION

3. Vasculitis

The pathogenesis of non-infectious vasculitis is:

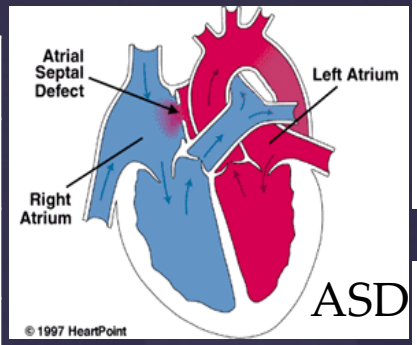
1. Immune complex deposition.
2. Antineutrophil cytoplasmic antibodies.
3. Anti-endothelial cell antibodies.

Variants:

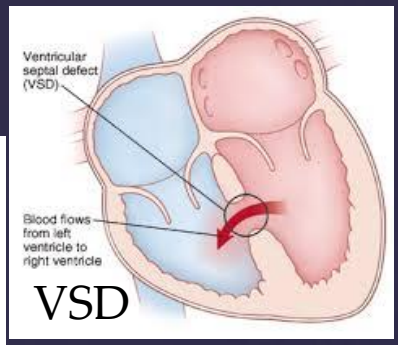
- Giant cell (temporal) arteritis; affecting mainly the temporal arteries with destructive giant cell granuloma.
- Takayasu's arteritis, involving the carotids and the subclavian arteries, with extension to the arch aorta, resulting in fibrosis of involved vessels (pulseless syndrome).
- Polyarteritis nodosa, involving medium sized arteries, frequently extending to involve the renal arteries, with necrotizing fibrinous inflammation.
- Kawasaki disease, happens in young children, involving the coronary arteries.
- Microscopic polyangiitis (leukocytoclastic vasculitis), occur in

4. Congenital Cardiac Diseases

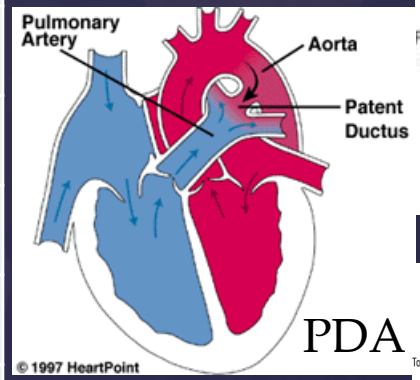
Malformation	%
Ventricular septal defect VSD	42
Atrial septal defect ASD	10
Pulmonary stenosis	8
Patent ductus arteriosus PDA	7
Tetralogy of Fallot TOF	5
Coarctation of aorta	5
Atrioventricular septal defect AVSD	4
Aortic stenosis	4
Transposition of great arteries TGA	4
Truncus arteriosus TA	1
Total anomalous pulmonary venous connection TAPVC	1
Tricuspid atresia	1



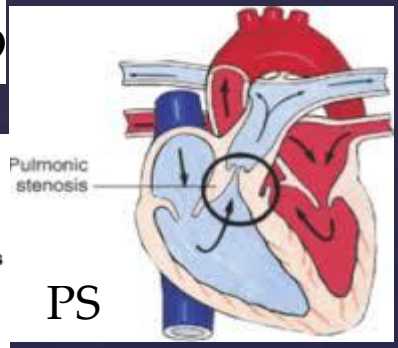
ASD



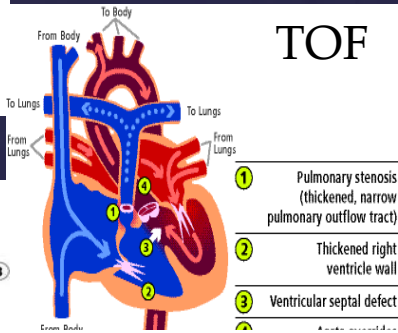
VSD



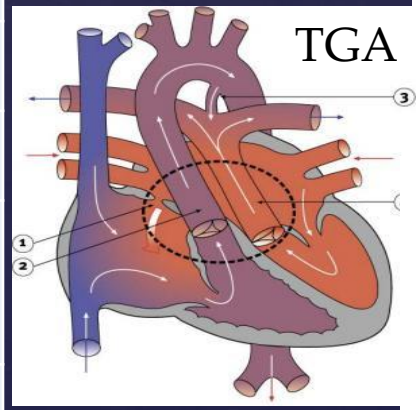
PDA

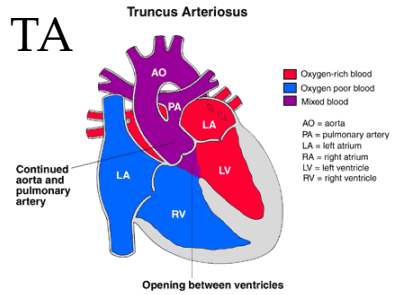


PS



TOF





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5. Ischæmic Heart Disease

Pathogenesis

IHD syndromes is diminished coronary perfusion relative to myocardial demand, owing largely to a complex and dynamic interaction among fixed

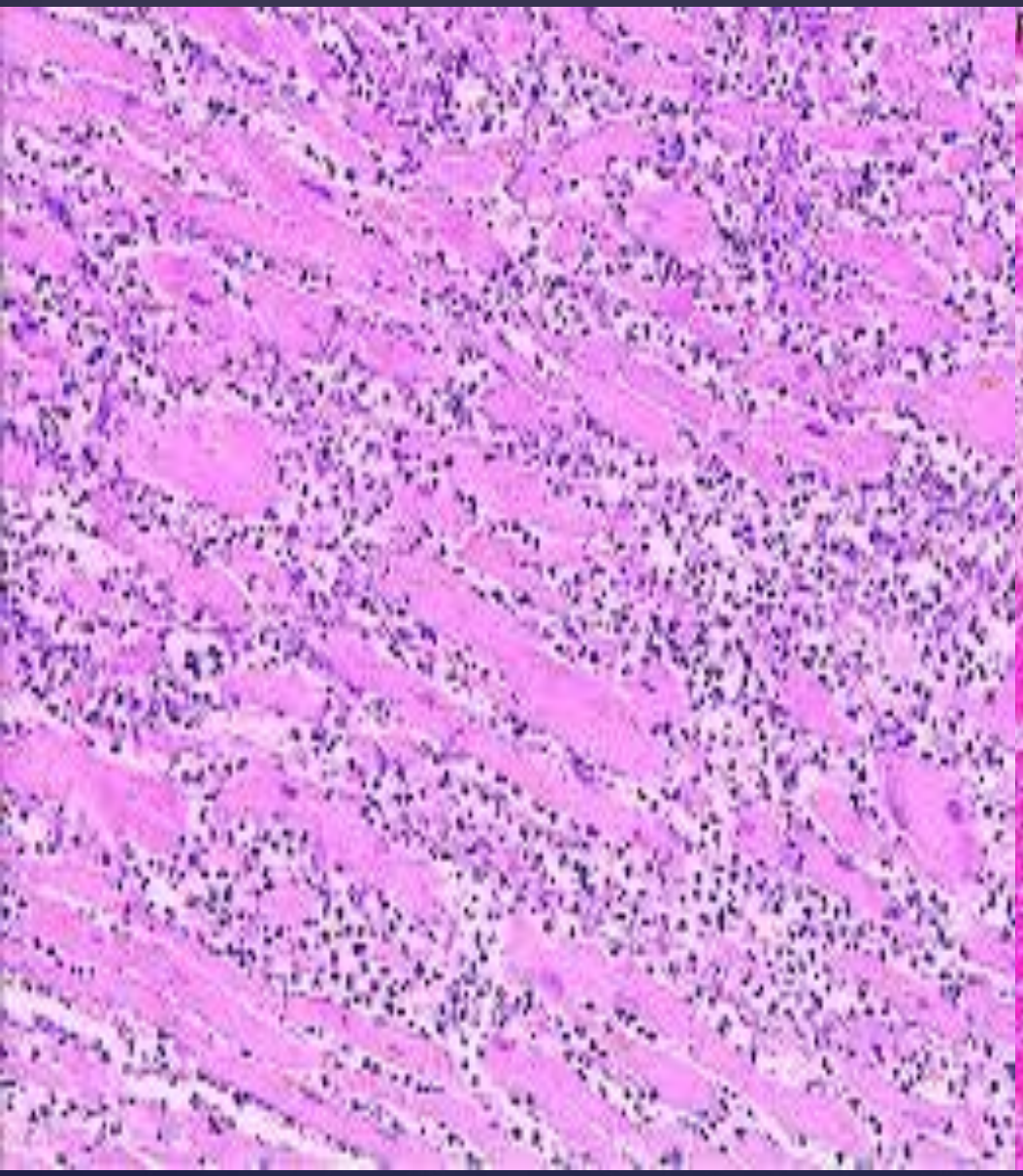
- atherosclerotic narrowing of the coronary arteries,
- intraluminal thrombosis overlying a disrupted atherosclerotic plaque,
- platelet aggregation,
- vasospasm.

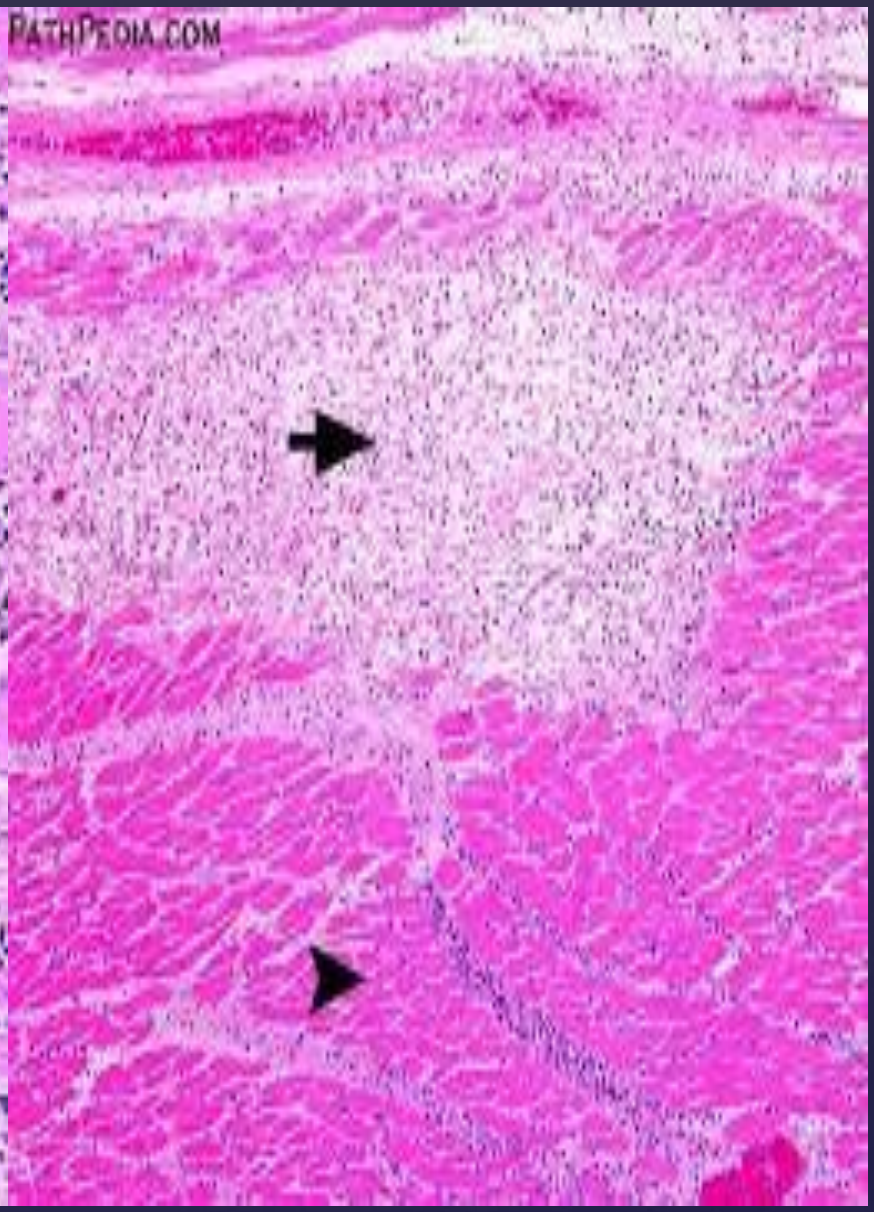
Obstruction of 75% of the coronary artery lumen by atheroma leads to symptoms on exertion,
while 90% obstruction causes symptoms even on rest (angina pectoris).
Acute plaque change leads to thrombosis and total occlusion of the coronary artery lumen with myocardial infarction. Acute plaque changes include:

1. Rupture/fissuring, exposing the highly thrombogenic plaque constituents.
2. Erosion/ulceration, exposing the thrombogenic subendothelial basement membrane to blood.
3. Hemorrhage into the atheroma, expanding its volume.

Morphologic changes in acute MI

Time	Gross Features	Light Microscope
Reversible Injury		
0-½ hr	None	None
Irreversible Injury		
½-4 hr	None	Usually none; variable waviness of fibers at border
4-12 hr	Occasionally dark mottling	Beginning coagulation necrosis; edema; hemorrhage
12-24 hr	Dark mottling	Ongoing coagulation necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; beginning neutrophilic infiltrate
1-3 days	Mottling with yellow-tan infarct center	Coagulation necrosis, with loss of nuclei; infiltrate of neutrophils
3-7 days	Hyperemic; central yellow-tan softening	Beginning disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border
7-10 days	Maximally yellow-tan and soft, with depressed red-tan margins	Well-developed phagocytosis of dead cells; early formation of fibrovascular granulation tissue at margins
10-14 days	Red-gray depressed infarct borders	Well-established granulation tissue with new blood vessels and collagen deposition
2-8 wk	Gray-white scar, progressive from border toward core of infarct	Increased collagen deposition, with decreased cellularity
>2 mo	Scarring complete	Dense collagenous scar

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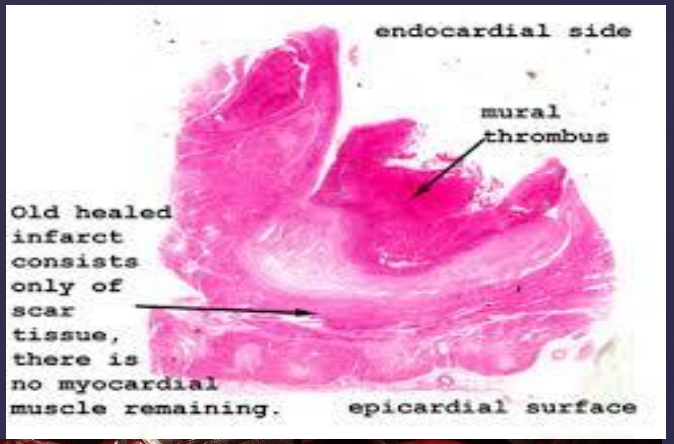
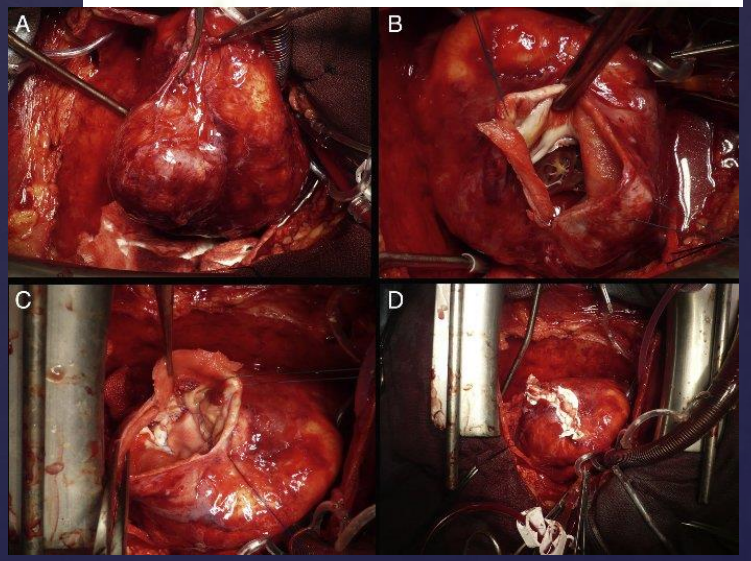
Consequences of MI

- Contractile dysfunction.
- Arrhythmias.
- Myocardial rupture.
- Pericarditis.
- Infarct extension.
- Infarct expansion.
- Mural thrombus.
- Ventricular aneurysm.
- Papillary muscle dysfunction.
- Progressive late heart failure.





6. Infective Endocarditis (IE):

colonization or invasion of the heart valves or the mural endocardium by a microbe, leading to the formation of bulky, friable vegetations, composed of thrombotic debris and organisms, often associated with destruction of the underlying cardiac tissues. IE can be classified into:

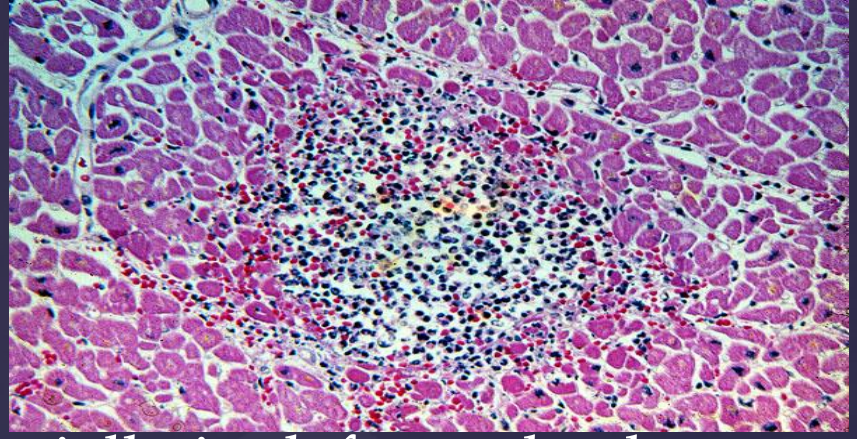
1. Acute endocarditis: destructive infection of previously normal heart valve by a highly virulent MQ leading to death of more than 50% of patients within few days. Producing necrotizing, ulcerative, invasive valvular infections that are difficult to cure by antibiotics and usually require surgery.

2. Subacute endocarditis: Caused by low virulent bacterial infecting an abnormal heart (deformed valves, VSD, ASD, etc…), pursuing a long course eventually to healing.

Etiology And Pathogenesis: Predisposing factors:

- Rheumatic heart disease.
- Myxomatous mitral valve.
- Degenerative calcific valvular stenosis.
- Neutropenia, and immunodeficiency
- Malignancy.
- Diabetes mellitus.
- Alcoholism & Intravenous drug abuse.

Causative microorganisms

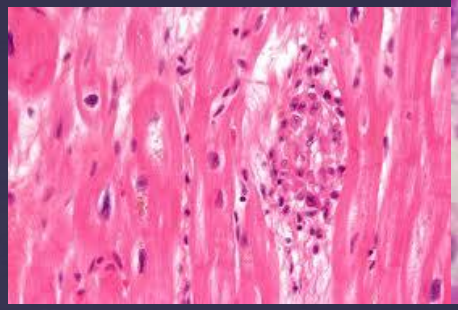


- *Streptococcus viridans* (50-60%).
- *Staphylococcus aureus* (10-20%), especially in deformed valves.
- Others (enterococci, *Hæmophilus, Acinetobacillus*, etc…).
- Gram negative bacilli and fungi.

Seeding of blood with microorganisms happens after dental extraction, surgical procedures, injection with contaminated needles or an occult source from the gut or oral cavity.

In both forms of the disease friable, bulky, and potentially destructive vegetations containing fibrin, inflammatory cells, and bacteria or other organisms are present on the heart valves, resulting in small *microabscesses* in the underlying myocardium and *septic emboli* to distant organs, resulting in *septic infarcts*.

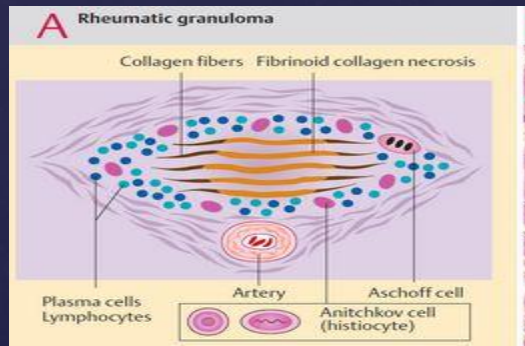
7. Rheumatic Heart Disease

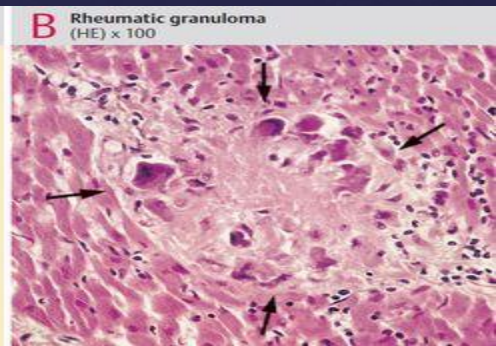


acute, immunologically mediated, multisystem inflammatory disease that occurs a few weeks following an episode of group A streptococcal pharyngitis. Acute rheumatic carditis during the active phase of RF may progress to chronic rheumatic heart disease (RHD). The incidence and mortality rate of RF have declined remarkably in many parts of the world over the past 30 years.

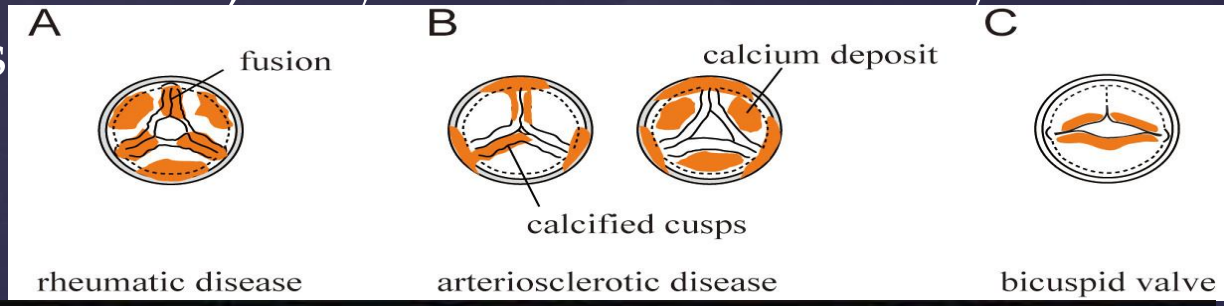
During acute RF, focal inflammatory lesions are found in various tissues. They are most distinctive within the heart, where they are called **Aschoff bodies**. They consist of foci of swollen eosinophilic collagen surrounded by lymphocytes (primarily T cells), occasional plasma cells, and plump macrophages called Anitschkow cells (pathognomonic for RF).

During acute RF, diffuse inflammation and Aschoff bodies may be found in any of the three layers of the heart- pericardium, myocardium, or endocardium- hence the lesion is called a pancarditis.
Pericarditis usually resolve spontaneously without sequalae.
Myocardial involvement is seen as scattered Aschoff bodies.
Involvement of the endocardium by inflammation results in fibrinoid necrosis and the formation of irregular vegetations along the line of closure of valves, due to precipitation of fibrin at sites of necrosis and cause little disturbance in valvular function.
Chronic RHD is characterized by organization of the acute inflammation and subsequent fibrosis. In particular, the valvular leaflets become thickened and retracted, causing permanent deformity.





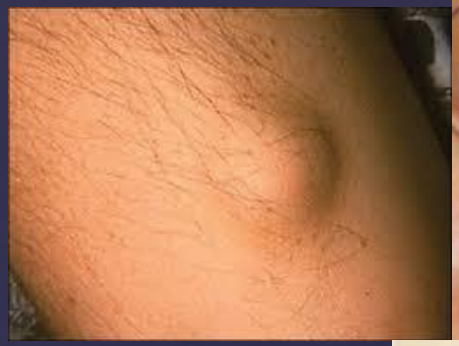
The cardinal anatomic changes of the mitral (or tricuspid) valve are **leaflet thickening**, commissural fusion and shortening, and thickening and fusion of the tendinous cords. In chronic disease, the mitral valve is virtually always abnormal, but involvement of another valve, such as the aortic, may be the most clinically important in some cases

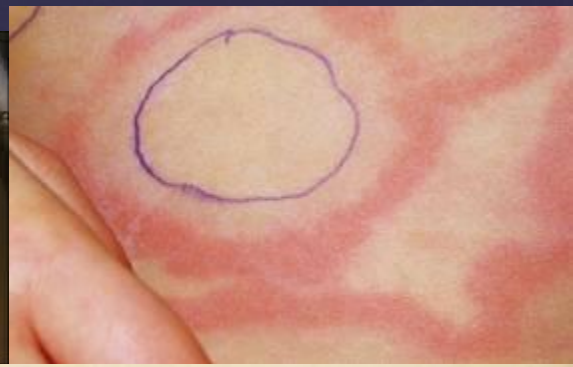


Pathogenesis

acute rheumatic fever is a hypersensitivity reaction induced by group A streptococci, but the exact pathogenesis remains uncertain despite many years of investigation.

It is thought that Ab directed against the M proteins of certain strains of streptococci cross-react with glycoprotein antigens in the heart, joints, and other tissues.





Clinical Features

characterized by

Major manifestations

(1) migratory polyarthritis of the large joints,
(2) carditis,
(3) subcutaneous nodules,
(4) erythema marginatum of the skin,
(5) Sydenham chorea, a neurologic disorder with involuntary purposeless, rapid movements.

After an initial attack, increased reactivation of the disease with subsequent pharyngeal infections, and the same manifestations are likely to appear with each recurrent attack. Carditis is likely to worsen with each recurrence, and damage is cumulative.