

Cardio II Study Guide

Blood Vessels

Normal

- **Intima** = inner of 3 concentric layers, consists of a single layer of endothelial cells (EC), minimal subendothelial connective tissue
 - **Endothelial cells uniquely contain Weibel-Palade bodies** (membrane bound organelles **containing vWF** and P-selectin)
- **Media** = middle layer; smooth muscle cells (SMC); separated from intima by *internal elastic lamina*; receives oxygen and nutrients by direct diffusion from vessel lumen
- **Adventitia** = outer layer; consists of connective tissue, nerve fibers, vasa vasorum; separated from media by *external elastic lamina*
 - **Vasa vasorum** = **small arterioles arising from outside vessels that course into outer 1/2 - 2/3 of the media of large and medium-sized vessels to nourish the media**

Endothelial cell properties and functions – Table 11-1, p514

- *Maintenance of permeability barrier*
 - Semipermeable
 - High bp, histamine cause widening of intercellular junctions
- **Elaboration of anticoagulant, antithrombotic, fibrinolytic regulators – very important for atherosclerosis**
 - **Prostacyclin** – endothelial *prostacyclin (PGI₂)* and **NO** inhibit platelet adherence to uninjured endothelium
 - **Thrombomodulin** – binds thrombin and converts it to an anticoagulant capable of activating *protein C* → protein C requires *protein S* (synthesized by endothelial cells) to *proteolytically cleave factors 5a and 8a*
 - **hyperhomocysteinemia** (acquired or inherited) → inhibition of antithrombin III and thrombomodulin → more clotting (arterial and venous thrombosis, also ↑ atherosclerosis)
 - **Heparin-like molecules** – interact w/ **antithrombin III** to inactivate several coag factors (thrombin; factors 9a, 10a, 11a, 12a)
 - **Plasminogen activator (t-PA)** – promotes **fibrinolytic activity** → clears fibrin deposits from endothelial surfaces → **produces D-dimers**
 - *Plasminogen is converted to plasmin by tPA*
 - *tPA (but not urokinase) requires fibrin as a cofactor*
- *Elaboration of prothrombotic molecules*
 - **vWF** – facilitates adhesion of platelets to subendothelial ECM; bridge btwn platelet surface receptors (**GpIb**, member of integrin family), **serum factors 5 and 9**, and exposed collagen
 - **von Willebrand disease** results from deficiencies or structural abnormalities of vWF → therefore it can be a **quantitative** or **qualitative** disorder
 - **Most common congenital bleeding disorder**
 - Us. autosomal dominant, males and females equally effected
 - Clinical characteristics – presents like platelet disorder but is NOT a platelet disorder
 - Increased bruising (typically petechiae)
 - Epistaxis (nose-bleeds)
 - **Normal platelet count**
 - Bleeding is moderate to severe (vWF also stabilizes factor 8)
 - **Plasminogen activator inhibitors (PAIs)** – depress fibrinolysis

- **PAIs are covalently bound and inhibited by serine protease inhibitors (SERPINS)**
- *Modulation of blood flow and vascular reactivity*
 - Vasoconstrictors: endothelin, ACE
 - **Vasodilators: NO, prostacyclin**
 - **NO** = pleiotropic mediator of inflammation, causes vasodilation & relaxation of SMC, reduces platelet aggregation and adhesion; synthesized from L-arginine by nitric oxide synthase (NOS)
 - Block NO production → **promote leukocyte rolling and adhesion**
 - Stimulate NO production or give exogenous NO → anti-inflammatory
- *Regulation of cell growth*
 - **Growth stimulators**
 - **PDGF (platelet derived growth factor)**
 - Source – platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells – **stored in platelet α granules**, released on platelet activation
 - Functions – **causes migration and activation/proliferation of fibroblasts, smooth muscle cells, and monocytes**; stimulates production of MMPs, fibronectin, and HA; **stimulates angiogenesis** and wound contraction; remodeling; inhibits platelet aggregation; regulates integrin expression
 - **CSF** (colony stimulating factor, assoc. w/ macrophages)
 - **FGF** (fibroblast growth factor)
 - Released FGFs assoc. w/ ECM heparan sulfate
 - Source – macrophages, mast cells, T cells, endothelial cells, fibroblasts, many tissues
 - Functions – wound repair: migration of macrophages, fibroblasts and endothelial cells in damaged tissues, migration of epithelium to form new epidermis; angiogenesis (FGF-2); hematopoiesis
 - Cell surface receptors w/ intrinsic tyrosine kinase activity
 - Growth inhibitors
 - Heparin
 - **TGF- β** (transforming growth factor)
 - Source – platelets, T cells, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts
 - Functions – inhibits growth of most epithelial cell types and leukocytes, blocks cells cycle; stimulates proliferation of fibroblasts and smooth muscle cells; potent fibrogenic agent, stimulates chemotaxis, enhances production of ECM material; strong anti-inflammatory effects

****Pro growth = PDGF, FGF, IFN, IL1. No growth = NO, TGF-B.****

Endothelial Cell (EC) Injury

- Denudation of ED → thrombosis, SMC proliferation
- **EC dysfunction = potentially reversible changes in the functional state of endothelial cells (altered phenotype) that occur in response to environmental stimuli that impairs vasoreactivity or induces surface changes (thrombogenic or adhesive);** can be a result of gene expression
- **EC activation = EC response to stimuli;** reflects alterations in gene expression and protein synthesis

• **EC dysfunction usually precedes EC activation**

Vascular SMC's

- Migrate to intima and proliferate following vascular injury
- Promoters of SMC growth = PDGF, endothelin-1, FGF, IFN- γ , IL-1
- Inhibitors of SMC growth = heparan sulfates, NO, TGF- β
- Also regulated by AGII, catecholamines, estrogen receptors, Osteopontin

Intimal Thickening

- Vascular injury (acute EC loss or chronic endothelial dysfunction) stimulates SMC growth
- **Formation of neointima = SMCs migrate from media to intima, multiply as intimal SMCs, and synthesize and deposit ECM**
- SMCs in intima lose capacity to contract, gain capacity to divide
- Intimal SMCs may return to nonproliferative state when EC layer is re-established
- **Exaggerated healing \rightarrow intimal thickening (hyperplasia) \rightarrow can cause Stenosis or occlusion**

Arteriovenous Fistulas	
Etiology	Abnormal communications btwn arteries and veins that arise as developmental defects, rupture of arterial aneurysm into adjacent vein, penetrating injuries that pierce walls of artery and vein, or from inflammatory necrosis of adjacent vessels
Epidemiology	Rare
Clinical Presentation	1) High-output cardiac failure 2) Hemorrhage (esp. in brain)

Atherosclerosis	
Most frequent and important form of arteriosclerosis	
Epidemiology	<ul style="list-style-type: none"> • #1 cause of mortality in the Western world (~ 1/2 of all deaths) – much less prevalent in Central and South America, Africa, Asia • Nonmodifiable Major Risk Factors <ul style="list-style-type: none"> ▪ AGE = dominant influence; incidence of MI \uparrow 5-fold btwn ages 40-60 ▪ MALES > females until 7th decade (then males = females) ▪ Genetic abnormalities <ul style="list-style-type: none"> • Homocystinuria (rare, inborn error of metabolism) – hyperhomocysteinemia can be caused by low folate and vitB intake • Homozygous familial hypercholesterolemia – often results in MI before age 20; caused by defects in LDL receptor \rightarrow inadequate hepatic uptake of LDL, markedly \uparrow circulating LDL • DIET, LIFESTYLE, and PERSONAL HABITS are potentially reversible/ controllable risk factors <ul style="list-style-type: none"> ▪ Hyperlipidemia, hypercholesterolemia (esp. LDL) – reduced by <i>statin</i> drugs (inhibit HMG-CoA reductase, enzyme required to cholesterol biosynthesis in liver) ▪ HTN ▪ Cigarette smoking ▪ Diabetes Mellitus – DM induces hypercholesterolemia; incidence of MI is twice as high in diabetics as in nondiabetics; atherosclerosis-induced gangrene of lower

	<p>extremities</p> <ul style="list-style-type: none"> • ↑ blood levels of <i>abnormal lipoprotein Lp(a)</i> correlated to ↑ coronary and cerebrovascular disease, independent of level of total cholesterol or LDL • <i>Risk factors are multiplicative</i> – 2 major risk factors increase risk 4X; 3 major risk factors increase risk 7X • <i>Hypothyroidism</i> – causes hypercholesterolemia
<i>American Heart Association classification</i>	<ul style="list-style-type: none"> • Type I (initial) lesion – isolated macrophage foam cells; growth by lipid accumulation; onset from 1st decade; clinically silent • Type II (fatty streak) lesion – mainly intracellular lipid accumulation; growth by lipid accumulation; onset from 1st decade; clinically silent • Type III (intermediate) lesion – type II changes and small extracellular lipid pools; growth by lipid accumulation; onset from 3rd decade; clinically silent • Type IV (atheroma) lesion – type II changes and core of extracellular lipid; growth by lipid accumulation; onset from 3rd decade; clinically silent or overt • Type V (fibroatheroma) lesion – lipid core and fibrolytic layer OR multiple lipid cores and fibrotic layers OR mainly calcific OR mainly fibrotic; growth by accelerated SMC and collagen increase; onset from 4th decade; can be clinically silent or overt • Type VI (complicated) lesion – surface defect, hematoma-hemorrhage, thrombus; growth by thrombosis, hematoma; onset from 4th decade; can be <p>*** know the classification and what is found in each***</p>
<i>Pathophysiology</i>	<ul style="list-style-type: none"> • Key processes = <i>intimal thickening, lipid accumulation</i> • <i>Response to Injury Hypothesis</i> – Fig 11-12, p525 <ul style="list-style-type: none"> ▪ <i>Chronic endothelial injury</i> = cornerstone of response-to-injury hypothesis; <i>However, early human lesions occur at sites of morphologically intact endothelium</i> <ul style="list-style-type: none"> • 2 most important determinants of endothelial alterations = hemodynamic disturbances & adverse effects of hypercholesterolemia • steady laminar flow protects against atherosclerosis ▪ Accumulation of lipoproteins (mainly LDL) ▪ Oxidation of lesional lipoproteins (mainly LDL) – oxidized LDL is ingested by macrophages thru scavenger receptor to form foam cells; increases monocytes accumulation in lesions; stimulates release of growth factors and cytokines; is cytotoxic to ECs and SMCs ▪ Adhesion of blood monocytes → macrophages → foam cells ▪ Adhesion of platelets ▪ Migration of SMCs from media into intima ▪ Proliferation of SMCs in intima → elaboration of ECM (mainly collagen) ▪ Enhanced accumulation of lipids w/in macrophages and SMCs

	<ul style="list-style-type: none"> • Infectious Hypothesis – <i>Chlamydia pneumoniae</i>, cytomegalovirus <ul style="list-style-type: none"> ▪ <i>C. pneumoniae</i> components have been detected in atherosclerotic lesions
<i>Gross Appearance</i>	<ul style="list-style-type: none"> • Abdominal aorta more involved than thoracic aorta • Coronary arteries > popliteal arteries > internal carotid arteries > circle of Willis
<i>Histological Morphology</i>	<ul style="list-style-type: none"> • Intimal lesions called atheromas or fatty plaques (= raised focal lesions initiating w/in intima w/ soft, yellow, grumous core of lipid, mainly cholesterol and cholesterol esters, covered by a firm, white fibrous cap) <ul style="list-style-type: none"> ▪ 3 principal components: <u>cells</u> (SMCs, macrophages, leukocytes); <u>ECM</u> (collagen, elastic fibers, proteoglycans); <u>lipid</u> (intracellular and extracellular) ▪ foam cells = macrophages and SMCs, lipid-laden ▪ Neovascularization around periphery of lesions • Calcification of coronary arteries → ↑ risk for coronary events • Advanced lesions at risk for rupture, ulceration, erosion of luminal surface → thrombus formation or release or microemboli • Hemorrhage INTO a plaque can induce plaque rupture • Thrombosis = most feared complication • Aneurysmal dilation may result from ATH-induced atrophy of media w/ loss of elastic tissue
<i>Typical Outcome of ATH</i>	<ul style="list-style-type: none"> • Major consequences = MI, CVA, aortic aneurysms, peripheral vascular disease • Other consequences = mesenteric occlusion, sudden cardiac death, chronic ischemic heart disease, ischemic encephalopathy
<i>Coronary Artery Disease</i>	<ul style="list-style-type: none"> • Figure 11-5, p517 • PreClinical Phase – us. young age (begins in childhood) – fatty streaks, fibrofatty plaque formation <ul style="list-style-type: none"> ▪ Primary Prevention = delay atheroma formation or cause regression of established lesions; pt's have never suffered a serious complication of atherosclerotic coronary artery disease • Clinical Phase – us. middle age to elderly – aneurysm and rupture; occlusion by thrombus; critical Stenosis → MI <ul style="list-style-type: none"> ▪ Secondary Prevention = intended to prevent recurrence of events such as MI in pt's w/ symptomatic disease

Familial Hypercholesterolemia (autosomal dominant) – possibly the most frequent mendelian disorder – mutated low-density lipoprotein (LDL) receptor gene (on chromosome 19) which is responsible for removing LDL from the blood → higher plasma cholesterol levels from birth → atherosclerosis at much earlier age

- VLDL secreted by liver into bloodstream (rich in triglycerides, lesser amt. of cholesterol esters) → cleaved by lipoprotein lipase at target tissue to release triglycerides and make IDL

- 50% of IDL taken up by LDL receptors on hepatocytes (LDL receptor recognizes apoprotein B-100 and apoprotein E on surface of IDL particle) → IDL recycled to generate VLDL
- 50% of IDL not taken up by liver, subjected to processing that removes triglycerides and apoprotein E → cholesterol-rich LDL produced → LDL receptor on hepatocytes binds LDL → complex is internalized via clathrin-coated pits → LDL enzymatically degraded in lysosomes, LDL receptor recycled to cell surface → cholesterol released into cytoplasm for membrane synthesis and as a regulator of cholesterol homeostasis
 - cholesterol suppresses cholesterol synthesis (inhibits HMG CoA reductase)
 - **statin drugs suppress intracellular cholesterol synthesis by inhibiting HMG CoA reductase → allows ↑ synthesis of LDL receptors → lowers plasma cholesterol levels**
- Mutated LDL receptor
 - *Defective LDL clearance*: heterozygous patients have reduced number of receptors (about 50%) → LDL taken up by tissue macrophages → formation of occlusive arterial plaques → acceleration of atherosclerosis and its complications. – *Fig 5-8, p157; Fig 5-9, p158*
 - *Increased synthesis of LDL* due to impaired IDL transport into liver (diverts greater proportion of plasma IDL into precursor pool for plasma LDL)

Monckeberg medial calcific sclerosis	
<i>Epidemiology</i>	Age > 50 years
<i>Morphology</i>	Calcific deposits in muscular arteries (in the media) , radiographically visible, often palpable, but do not encroach on vessel lumen
<i>Clinical Presentation</i>	Often hard to distinguish from normal aging changes

Arteriosclerosis	
<i>Morphology</i>	<ul style="list-style-type: none"> • Hyaline or hyperplastic changes in walls of small arteries and arterioles <ul style="list-style-type: none"> ▪ Hyaline type – deposition of BM and plasma proteins cause thickening of arterial wall ▪ Hyperplastic type – fibrocellular intimal thickening in concentric layers (‘onion-skinning’)
<i>Clinical Presentation</i>	<ul style="list-style-type: none"> • Hyaline arteriosclerosis most often assoc. w/ benign HTN, benign Nephrosclerosis, and long-standing diabetes mellitus • Hyperplastic arteriosclerosis assoc. w/ malignant HTN

Aneurysm = localized abnormal dilation of a blood vessel or wall of the heart

- **True aneurysm** = bounded by arterial wall components or attenuated wall of heart
 - includes atherosclerotic, syphilitic, and congenital aneurysms and left ventricular aneurysm that can follow MI
 - all wall constituents are in place
 - **2 MOST COMMON CAUSES of aortic aneurysms = atherosclerosis & cystic medial degeneration of arterial media**
 - *Mycotic aneurysm* – due to infection of major artery; thrombosis and rupture are possible complications; may originate from embolization and arrest of septic embolus (us. as complication of infective endocarditis) OR as an extension of adjacent suppurative process OR by circulating organisms directly infecting the arterial wall

- ***Pseudoaneurysm*** = breach in vascular wall leading to extravascular Hematoma that freely communicates w/ intravascular space (“pulsating hematoma”)
 - lesion is between layers of the arterial wall
 - MOST COMMON pseudoaneurysm = post-MI rupture contained by pericardial adhesion

Dissection = blood enters the wall of the artery; does not always arise in an aneurysm

Abdominal Aortic Aneurysm (AAA)	
<i>Etiology</i>	<ul style="list-style-type: none"> • Genetic susceptibility to AAA • Defects in connective tissue – Marfan Syndrome • Disrupted balance in aortic remodeling <ul style="list-style-type: none"> ▪ MMPs expressed at elevated levels compared to normal vessel wall (↑ proteolysis of ECM proteins) ▪ TIMPs (tissue inhibitors of MMPs) expressed at decreased levels in aortic aneurysms
<i>Epidemiology</i>	<ul style="list-style-type: none"> • Atherosclerotic aneurysms occur MOST FREQUENTLY in abdominal aorta, us. below renal arteries • Age > 50 • MEN > women
<i>Pathophysiology</i>	Atherosclerosis → plaque rupture, ulceration, erosion → aneurysmal dilation
<i>Gross Morphology</i>	<ul style="list-style-type: none"> • Can be saccular or fusiform • Atheromatous ulcers covered by granular mural thrombi • Commonly accompanied by smaller fusiform or saccular dilations of iliac arteries
<i>Histological Morphology</i>	<ul style="list-style-type: none"> • Inflammatory AAA's – dense periaortic fibrosis containing abundant inflammatory reaction rich in lymphocytes and plasma cells, many macrophages, often giant cells • Mycotic AAA's – atherosclerotic AAAs that have been infected by circulating organisms, particularly in bacteremia from primary <i>Salmonella gastroenteritis</i>
<i>Clinical Course</i>	<ul style="list-style-type: none"> • Rupture into peritoneal cavity → potentially fatal hemorrhage • Obstruction of vessel (iliac, renal, mesenteric, vertebral branches) → ischemic tissue injury • Embolism from atheroma or mural thrombus • Impingement on adjacent structure → compression of ureter, erosion of vertebrae, etc. • Presentation as abdominal mass (often palpably pulsating) w/ bruit
<i>Other</i>	<ul style="list-style-type: none"> • Risk of rupture is directly related to size of aneurysm • The most important clinical factor affecting aneurysm growth is bp (La Place's Law = wall tension is proportional to diameter and internal pressure) • Rupture = bad, risk assoc with size, 0-4 cm = 0% per yr, 4-5 cm = 1% per yr, 5-6 = 11% per yr, 6+ = 25% per yr. Growth dependent on BP (know the percentages there was a question on this!)

Thoracic aortic aneurysms (regardless of etiology) cause:

- 1) encroachment on mediastinal structures
- 2) respiratory difficulties
- 3) difficulty swallowing due to compression of esophagus
- 4) persistent cough due to irritation of or pressure on recurrent laryngeal nerves
- 5) pain caused by erosion of bone (ribs or vertebral bodies)
- 6) cardiac disease (aortic valve dilation w/ valvular insufficiency; narrowing of coronary ostia causing MI)
- 7) rupture

Syphilitic (Luetic) Aneurysm	
<i>Etiology</i>	Tertiary syphilis → obliterative endarteritis of vasa vasorum leads to aneurysmal dilation
<i>Pathophysiology</i>	<ul style="list-style-type: none"> • Obliterative endarteritis of vasa vasorum, rimmed by infiltrate of lymphocytes and plasma cells (<u>syphilitic aortitis</u>) → ischemic injury of aortic media, patchy loss of medial elastic fibers and SMCs → inflammation, scarring → contraction of scars can cause “tree-barking” appearance (wrinkling of intervening segments of aortic intima) • Luetic involvement of aorta favors superimposed atheromatosis of aortic root (unusual location for typical atherosclerosis) → can envelop and occlude <u>coronary ostia</u> • Luetic aortitis may also cause aortic valve ring dilation → valvular insufficiency → LVH (“cor bovinum” = cow’s heart, up to 1000 gm)

Aortic Dissection (Dissecting Hematoma)	
<i>Definition</i>	Dissection of blood btwn and along laminar planes of media w/ formation of blood-filled channel w/in aortic wall, which often ruptures outward causing massive hemorrhage
<i>Etiology</i>	<ul style="list-style-type: none"> • > 90% occur in MEN ages 40-60 w/ antecedent HTN <ul style="list-style-type: none"> ▪ HTN is the MAJOR RISK FACTOR for dissection overall
<i>Morphology</i>	<p><u>Spontaneous dissection</u></p> <ul style="list-style-type: none"> • Intimal tear extends into but not through media of ascending aorta, us. w/in 10 cm of aortic valve • Tears are us. transverse or oblique w/ sharp, jagged edges • Dissecting Hematoma spreads btwn middle and outer thirds and often ruptures out → massive hemorrhage • Double-barreled aorta w/ false channel results from rupture back into lumen • Most frequent preexisting histologically detectable lesion = medial degeneration (<u>cystic medial degeneration</u>) <ul style="list-style-type: none"> ▪ Characterized by elastic tissue fragmentation; separation of elastic and fibromuscular elements of tunica media ▪ Often accompanies Marfan Syndrome
<i>Clinical Course</i>	<ul style="list-style-type: none"> • <u>Proximal lesions (type A)</u> involve ascending portion only or both ascending and descending aorta – harder to repair surgically • <u>Distal lesions (type B)</u> do not involve ascending portion, us. begin distal to subclavian • Classic symptoms = sudden onset of excruciating pain beginning

	in anterior chest and radiating to back
Typical Outcome of Aortic Dissection	<ul style="list-style-type: none"> • MOST COMMON CAUSE OF DEATH = rupture of dissection outward into pericardial, pleural, or peritoneal cavities

Marfan Syndrome (*autosomal dominant*) – disorder of the connective tissues of the body-disease results from mutations in the **fibrillin-1** (FBN1) gene (extracellular glycoprotein) found on **chromosome 15q21.1**

- Skeletal abnormalities – **long extremities, long tapering fingers and toes, lax joint ligaments of hands and feet, bossing of frontal eminences, prominent supraorbital ridges**
 - Ocular changes – **ectopia lentis** (bilateral subluxation or dislocation of the lens)
 - Cardiovascular lesions – most life-threatening features; **mitral valve prolapse (“floppy” valve)** → mitral regurgitation; progressive dilation of aortic valve ring and root of aorta (**cystic medionecrosis, aortic dissection**) → severe aortic incompetence

Ehlers-Danlos Syndromes (EDS) – disorder of synthesis or structure of fibrillar collagen, inadequate tensile strength of connective tissue – all 3 modes of mendelian inheritance – characterized by **hyperextensible skin, hypermobile joints, skin extremely fragile and vulnerable to trauma, serious internal complications**

- **Vascular type = abnormalities of type III collagen, autosomal dominant** – characterized by spontaneous rupture of blood vessels and intestines

Vasculitides = inflammatory disorders affecting the body’s vasculature

- 2 MOST COMMON mechanisms of vasculitis = direct invasion of vascular walls by infectious pathogens; immune-mediated mechanisms
- Noninfectious vasculitis mechanisms = (1) immune complex deposition, (2) antineutrophil cytoplasmic antibodies, (3) anti-endothelial cell antibodies
 - Immune complex deposition → local Arthus phenomenon, serum sickness
 - ANCA = heterogeneous group of autoAbs directed against enzymes mainly found w/in azurophilic granules in neutrophils, lysosomes of monocytes, and in ECs
 - **c-ANCA shows cytoplasmic staining; most common target Ag = proteinase-3 (PR3), a neutrophil granule constituent**
 - **p-ANCA shows perinuclear staining; us. specific for myeloperoxidase (MPO)**
 - Antibodies to ECs – assoc. w/ SLE and Kawasaki disease

Giant Cell (Temporal) Arteritis	
Etiology	MOST COMMON form of systemic vasculitis in adults <ul style="list-style-type: none"> • Principally affects arteries in the head – esp. temporal arteries – also vertebral & ophthalmic arteries and aorta • Ophthalmic arterial involvement may lead to permanent blindness
Epidemiology	<ul style="list-style-type: none"> • Age > 50 years • Predilection for superficial temporal arteries
Pathophysiology	<ul style="list-style-type: none"> • Granulomatous nature, assoc. w/ certain human leukocyte DR antigens (HLA-DR)
Morphology	<ul style="list-style-type: none"> • Acute and chronic, often granulomatous, inflammation of arteries of large to small size • Segments of affected arteries develop nodular thickenings w/

	<p>reduction of lumen, may become thrombosed</p> <ul style="list-style-type: none"> • Common pattern: granulomatous inflammation of inner half of media centered on internal elastic membrane marked by mononuclear infiltrate, multinucleate giant cells of both foreign body and Langhans type (present in two thirds of cases), fragmentation of internal elastic lamina • Healed stage = collagenous thickening of vessel wall; organization of luminal thrombus sometimes transforms artery into fibrous cord; may be difficult to distinguish from aged-related changes
Clinical Presentation	<ul style="list-style-type: none"> • Symptoms can be vague and constitutional (fever, fatigue, weight loss) w/out localizing signs or symptoms, ***polymyalgia rheumatica (present by not being able to get out of chair) • Symptoms can be facial pain or unilateral headache, often most intense along course of superficial temporal artery, may be painful to palpation • Ocular symptoms (assoc. w/ involvement of ophthalmic artery) are more serious, appear abruptly in ~ 1/2 of patients, range from diplopia to transient or complete vision loss (total blindness = medical emergency) • ***Diagnosis depends on temporal artery segmental biopsy and histologic confirmation • Treatment w/ anti-inflammatory agents generally very effective

Takayasu arteritis	
Etiology	<ul style="list-style-type: none"> • High frequency of the HLA haplotype A24-B52-DR2 found in Japanese pts.
Epidemiology	Predominantly seen in FEMALES, age < 40 years
Pathophysiology	<ul style="list-style-type: none"> • Involvement of aortic root may cause dilation → aortic valve insufficiency • Narrowing of coronary ostia → MI
Morphology	<ul style="list-style-type: none"> • Granulomatous vasculitis of medium and larger arteries (may be indistinguishable from giant cell arteritis) – vasculitis and subsequent fibrous thickening of aorta, particularly aortic arch and its branches, w/ narrowing or virtual obliteration of origins or more distal portions
Clinical Presentation	<ul style="list-style-type: none"> • Characterized principally by ocular disturbances (visual defects, retinal hemorrhages, total blindness) and*** marked weakening of the pulses in the upper extremities (pulseless disease) • Also – HTN; neurologic deficits; claudication of the legs; pulmonary HTN • Diagnosis via arteriography

Polyarteritis Nodosa (PAN)	
Epidemiology	<ul style="list-style-type: none"> • Although a disease of young adults, classic PAN may occur in children and older individuals; MALES > females
Pathophysiology	<ul style="list-style-type: none"> • Systemic vasculitis of small or medium-sized muscular arteries (not arterioles, capillaries, or venules), typically involves renal & visceral vessels but <i>sparing pulmonary circulation and glomeruli of kidneys</i> • Type III hypersensitivity – Immune complex deposition, activation of mono's and poly's • Strong association with HBV

	<ul style="list-style-type: none"> • NO ANCA
<i>Morphology</i>	<ul style="list-style-type: none"> • Segmental transmural necrotizing inflammation of arteries of medium to small size (most frequently kidneys, heart, liver, GI tract) • Segmental erosion w/ weakening of arterial wall due to inflammatory process → aneurysmal dilation or localized rupture • Acute phase characterized by transmural inflammation of arterial wall w/ neutrophils, eosinophils, and mononuclear cells, frequently accompanied by fibrinoid necrosis • Later → fibrous thickening of the vessel wall, may extend into adventitia; firm nodularity sometimes marks lesions • Particularly characteristic of PAN is that all stages of activity may coexist in different vessels or even within the same vessel
<i>Clinical Presentation</i>	<ul style="list-style-type: none"> • Ischemia and infarction of affected tissues and organs • Most common manifestations are malaise, fever of unknown cause, and weight loss; hypertension; abdominal pain and melena (bloody stool) due to vascular lesions in GI tract; diffuse muscular aches and pains; peripheral neuritis, predominantly motor • Renal arterial involvement is often prominent and is a major cause of death
<i>Typical Outcome</i>	<ul style="list-style-type: none"> • Disease is fatal in most cases

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)	
<i>Epidemiology</i>	<ul style="list-style-type: none"> • Affects large, medium-sized, and small arteries; often involves coronary arteries • Us. in young children and infants
<i>Pathophysiology</i>	<ul style="list-style-type: none"> • T-cell and macrophage activation to unknown Ag, secretion of cytokines, polyclonal B-cell hyperactivity, and formation of autoAbs to ECs and SMCs → acute vasculitis • Speculation: in genetically susceptible persons, a variety of common infectious agents (most likely viral) may trigger the disease
<i>Morphology</i>	Vasculitis is PAN-like, with necrosis and pronounced inflammation affecting the entire thickness of the vessel wall, but fibrinoid necrosis is usually less prominent in Kawasaki disease
<i>Clinical Presentation</i>	<ul style="list-style-type: none"> • Fever, conjunctival and oral erythema and erosion, edema of the hands and feet, erythema of the palms and soles, a skin rash often with desquamation, and enlargement of cervical lymph nodes • 20% of pts. develop cardiovascular sequelae (asymptomatic vasculitis of coronary arteries, coronary artery ectasia, aneurysm formation, giant coronary artery aneurysms (7 to 8 mm) with rupture or thrombosis, MI, sudden death)

Wegener Granulomatosis	
<i>Etiology</i>	<ul style="list-style-type: none"> • A form of microscopic polyangiitis • Presence of granulomas and dramatic response to immunosuppressive therapy strongly support an immunologic mechanism, perhaps of the cell-mediated type
<i>Epidemiology</i>	MALES > females Age 40-60 y.o. peak incidence
<i>Pathophysiology</i>	c-ANCA present in up to 95% of patients

Morphology	<ul style="list-style-type: none"> • Necrotizing vasculitis characterized by the triad of (1) acute necrotizing granulomas of UR tract (ear, nose, sinuses, throat), LR tract (lung), or both; (2) necrotizing or granulomatous vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries), most prominent in the lungs and upper airways; and (3) renal disease (<i>focal necrotizing, often crescentic, glomerulitis</i>) • UR lesions = range from inflammatory sinusitis (mucosal granulomas) to ulcerative lesions of the nose, palate, or pharynx, rimmed by necrotizing granulomas and accompanying vasculitis <ul style="list-style-type: none"> ▪ Alveolar hemorrhage may be prominent in lung lesions • Renal lesions = 2 types <ul style="list-style-type: none"> ▪ Milder or early forms = acute focal proliferation and glomerular necrosis, thrombosis of isolated glomerular capillary loops (focal necrotizing glomerulonephritis) ▪ More advanced glomerular lesions = diffuse necrosis, proliferation, and crescent formation (crescentic glomerulonephritis)
Clinical Presentation	<ul style="list-style-type: none"> ○ Typical clinical features = persistent pneumonitis w/ bilateral nodular and cavitory infiltrates (95%), chronic sinusitis (90%), mucosal ulcerations of the nasopharynx (75%), evidence of renal disease (80%) ○ Other features = skin rashes, muscle pains, articular involvement, mononeuritis or polyneuritis, fever
Typical Outcome	<ul style="list-style-type: none"> • Focal renal lesions → hematuria and proteinuria responsive to immunosuppressive therapy • Diffuse disease → rapidly progressive renal failure

Churg-Strauss syndrome	
Etiology	<ul style="list-style-type: none"> • A form of microscopic polyangiitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries) = allergic granulomatosis and angitis • Strong association with allergic rhinitis, bronchial asthma, and eosinophilia
Pathophysiology	p-ANCA present in 50%
Morphology	<ul style="list-style-type: none"> • Vascular lesions may be histologically similar to those of classic PAN or microscopic polyangiitis, but characteristically have necrotizing vasculitis accompanied by granulomas w/ eosinophilic necrosis • Vessels in lung, heart, spleen, peripheral nerves, and skin frequently involved by intravascular and extravascular granulomas • Early, prevasculitic phase marked by tissue infiltration by eosinophils w/out overt vasculitis may be present in some cases

Microscopic Polyangiitis (Microscopic Polyarteritis, Leukocytoclastic Vasculitis)	
Etiology	Immunologic reaction to an antigen such as drugs (e.g., penicillin), microorganisms (e.g., streptococci), heterologous proteins, and tumor antigens
Pathophysiology	p-ANCA present in 70% of pts.
Morphology	• <i>generally affects arterioles, capillaries, and venules—vessels smaller</i>

	<p><i>than those involved in PAN</i></p> <ul style="list-style-type: none"> • In contrast to PAN, all lesions tend to be of the same age • In contrast to PAN, necrotizing glomerulonephritis (90% of patients) and pulmonary capillaritis are particularly common • Lesions often histologically similar to those of PAN • In contrast to PAN, muscular and large arteries are usually spared; thus, macroscopic infarcts similar to those seen in PAN are uncommon • Same spectrum of manifestations as Wegener granulomatosis, but granulomatous inflammation is absent • Segmental fibrinoid necrosis of the media may be present, but in some lesions change is limited to infiltration w/ neutrophils, which become fragmented as they follow the vessel wall (leukocytoclasia) = leukocytoclastic angiitis (LCA), most commonly found in postcapillary venules
Clinical Presentation	<ul style="list-style-type: none"> • Typically presents as "palpable purpura" involving skin, or involvement of mucous membranes, lungs, brain, heart, gastrointestinal tract, kidneys, and muscle • Diagnosis by skin biopsy • Major clinical features are hemoptysis, arthralgia, abdominal pain, hematuria, proteinuria, hemorrhage, and muscle pain or weakness
Typical Outcome	most patients respond well simply to removal of the offending agent

Thromboangiitis Obliterans (Buerger Disease)	
Etiology	<p><u>Genetic influences</u></p> <ul style="list-style-type: none"> • ↑ prevalence of HLA-A9 and HLA-B5 • Far more common in Israel, Japan, and India than in US and Europe
Epidemiology	Historically CIGARETTE smoking males < 35 y.o. (incidence in women is rising)
Morphology	<ul style="list-style-type: none"> • Characterized by segmental, thrombosing, acute and chronic inflammation of medium-sized and small arteries, principally tibial and radial arteries and sometimes secondarily extending to veins and nerves of extremities • Acute and chronic inflammation permeates arterial walls, accompanied by thrombosis of lumen, may undergo organization and recanalization • Thrombus contains small microabscesses with central focus of neutrophils surrounded by granulomatous inflammation
Clinical Presentation	<ul style="list-style-type: none"> • Later complications = chronic ulcerations of toes, feet, or fingers; frank gangrene in some patients • Assoc. w/ Raynaud phenomenon

Systemic Diseases assoc. w/ vasculitis

- SLE – anti-inflammatory therapy
- Antiphospholipid antibody syndrome – antithrombotic/anticoagulant therapy
- Rheumatoid arthritis – small and medium-sized arteries; visceral infarction; aortitis

Henoch-Schonlein Purpura	
Epidemiology	Most common in children 3-8 years old, onset often follows upper respiratory infection , most have excellent prognosis
Pathophysiology	<ul style="list-style-type: none"> • IgA deposited in glomerular mesangium → IgA nephropathy & Henoch-Schonlein Purpura are spectra of the same disease • Skin lesions = subepidermal hemorrhages, necrotizing vasculitis

	in dermis (arterioles, capillaries, venules)
Clinical Presentation	<ul style="list-style-type: none"> • Purpuric skin lesions characteristically involving extensor surfaces of arms, legs, buttocks; abdominal manifestations incl. pain, vomiting, GI bleeding; nonmigratory arthralgias; renal abnormalities • <i>Renal manifestations in ~30% of patients</i> <ul style="list-style-type: none"> ➤ <i>Asymptomatic hematuria</i>

Raynaud Phenomenon	
Definition	Paroxysmal pallor or cyanosis of digits of hands or feet and, infrequently, tips of the nose or ears (acral parts) owing to cold-induced vasoconstriction of digital arteries, precapillary arterioles, and cutaneous arteriovenous shunts
Etiology	<ul style="list-style-type: none"> • Primary Raynaud phenomenon = exaggeration of normal central and local vasomotor responses to cold or emotion; pt otherwise healthy • Secondary Raynaud Phenomenon = arterial insufficiency of the extremities caused by various underlying conditions, including SLE, systemic sclerosis (scleroderma), atherosclerosis, or Buerger disease
Epidemiology	<ul style="list-style-type: none"> • Primary Raynaud Phenomenon: median age is 14 years, females • Secondary Raynaud: age of onset >30 years, more severe episodes, associated skin lesions, and clinical features of connective tissue disease

Varicose Veins	
Definition	abnormally dilated, tortuous veins produced by prolonged, increased intraluminal pressure and loss of vessel wall support
Epidemiology	<ul style="list-style-type: none"> • > 50 years old, obese individuals, women
Pathophysiology	superficial veins of the upper and lower leg are the main sites of involvement
Morphology	<ul style="list-style-type: none"> • Intraluminal thrombosis and valvular deformities (thickening, rolling, and shortening of the cusps) • Variations in thickness of vein wall caused by dilation in some areas and by compensatory hypertrophy of SMCs and subintimal fibrosis in others • Phleboscclerosis = elastic tissue degeneration, spotty calcifications w/in media
Clinical Presentation	<ul style="list-style-type: none"> • Venous stasis, congestion, edema, pain, and thrombosis • Persistent edema in the extremity, stasis dermatitis, and poorly healing wounds and infections that may become chronic varicose ulcers

Thrombophlebitis & Phlebothrombosis	
Etiology	<ul style="list-style-type: none"> • <i>Cardiac failure, neoplasia, pregnancy, obesity, the postoperative state, and prolonged bed rest or immobilization are the most important clinical predispositions</i> • Assoc. w/ genetic hypercoagulability syndromes • Hypercoagulability can be a paraneoplastic syndrome assoc. w/ adenocarcinomas of the pancreas, colon, or lung <ul style="list-style-type: none"> ▪ Migratory thrombophlebitis (Trousseau sign) – thromboses appear in one site, disappear, followed by thromboses in other veins (seen in pancreatic cancer)
Epidemiology	Deep leg veins account for more than 90% of cases of thrombophlebitis and

	<i>phlebothrombosis</i>
Clinical Presentation	Us. asymptomatic but pain can be elicited by pressure over affected veins, squeezing the calf muscles or forced dorsiflexion of the foot (Homan sign)
Typical Outcome	<i>Pulmonary embolism is a common and serious clinical sequel to deep leg vein thrombosis</i>
Other	<ul style="list-style-type: none"> • <i>Plegmasia alba dolens (painful white leg)</i> = variant of primary phlebothrombosis; refers to iliofemoral venous thrombosis occurring in pregnant women prior to or following delivery (also called "milk leg") <ul style="list-style-type: none"> ▪ Thrombus (predisposed by stasis caused by pressure of the gravid uterus and hypercoagulable state during pregnancy) initiates phlebitis → inflammatory response induces lymphatic blockage w/ painful swelling

Superior and Inferior Vena Caval Syndromes	
Etiology	<ul style="list-style-type: none"> • Superior – us. caused by neoplasms that compress or invade superior vena cava, most commonly a primary bronchogenic carcinoma or mediastinal lymphoma • Inferior – may be caused by neoplasms that either compress or penetrate walls of the inferior vena cava or thrombus from femoral or iliac vein that propagates upward; certain neoplasms (particularly hepatocellular carcinoma and renal cell carcinoma) grow within veins, extend into inferior vena cava and into RA
Clinical Presentation	<ul style="list-style-type: none"> • Superior – distinctive clinical complex manifested by dusky cyanosis and marked dilation of veins of head, neck, and arms; pulmonary vessels commonly compressed → respiratory distress • Inferior – marked edema of legs, distention of superficial collateral veins of lower abdomen, and massive proteinuria (when renal veins are involved)

Tumors

Hemangioma (benign)	
Characteristics	<ul style="list-style-type: none"> • Majority are superficial lesions, often on head or neck; may occur internally, with nearly 1/3 in liver • Malignancy is rare
Epidemiology	7% of all benign tumors in infancy and childhood
Morphology/ Clinical Presentation	<ul style="list-style-type: none"> • Angiomatosis = hemangioma involving large segment of body • Capillary hemangiomas = largest single type of vascular tumor; most common in the skin, subcutaneous tissues, and mucous membranes of oral cavities and lips; may also occur in liver, spleen, and kidneys <ul style="list-style-type: none"> ▪ Juvenile hemangioma = "strawberry type" of capillary hemangioma of skin of newborns; may be multiple, grows rapidly in the first few months, begins to fade when child is 1-3 y.o., regresses by age 7 in 75-90% of cases ▪ Bright red to blue; level w/ surface of skin or slightly elevated; have intact covering epithelium ▪ Us. lobulated but unencapsulated aggregates of closely packed, thin-walled capillaries

	<ul style="list-style-type: none"> • Cavernous hemangiomas = same age and anatomic distribution as capillary hemangiomas, but are us. larger, less well circumscribed, and more frequently involve deep structures <ul style="list-style-type: none"> ▪ Red-blue, soft, spongy mass 1-2 cm in diameter ▪ Histologically, mass is sharply defined but not encapsulated; made up of large, cavernous vascular spaces, partly or completely filled with blood separated by scant connective tissue stroma ▪ Common assoc. w/ intravascular thrombosis, dystrophic calcification • Pyogenic Granuloma (Lobular Capillary Hemangioma) – rapidly growing exophytic red nodule attached by stalk to skin and gingival or oral mucosa <ul style="list-style-type: none"> ▪ Bleeds easily, often ulcerated ▪ 1/3 develop after trauma ○ Granuloma gravidarum = type of pyogenic granuloma that occurs in gingiva of 1% of pregnant women and regresses after delivery <ul style="list-style-type: none"> ▪ Highlight role of estrogen in vascular growth and proliferation
Other	von Hippel-Lindau disease – cavernous hemangiomas occur w/in cerebellum, brain stem, and eye; similar angiomatous lesions or cystic neoplasms occur in pancreas and liver and other visceral neoplasms

Lymphangioma (benign)	
Definition	Benign lymphatic analog of hemangiomas
Morphology/ Clinical Presentation	<ul style="list-style-type: none"> • Lymphangioma Circumscriptum (Capillary Lymphangioma) = tend to occur subcutaneously in head and neck region and in axilla; slightly elevated or sometimes pedunculated lesions, 1-2 cm in diameter; blister-like blebs filled w/ exudates – distinguished from capillary channels only by absence of blood cells • Cavernous lymphangioma (cystic hygroma) = occurs in children in neck or axilla (rarely, retroperitoneally); occasionally achieve considerable size (up to 15 cm in diameter) and may fill axilla or produce gross deformities in and about neck – composed of massively dilated, cystic lymphatic spaces lined by endothelial cells, separated by scant intervening connective tissue stroma that often contains lymphoid aggregates <ul style="list-style-type: none"> ▪ Cystic hygromas of the neck occur in Turner syndrome

Glomus Tumor, Glomangioma (benign)	
Characteristics	Biologically benign but often exquisitely painful tumor that arises from modified SMCs of glomus body
Morphology/ Clinical Presentation	<ul style="list-style-type: none"> • Most commonly found in the distal portion of the digits • Us. small, slightly elevated, rounded, red-blue, firm nodules; may appear as minute foci of fresh hemorrhage under the nail • Histologically: branching vascular channels separated by connective tissue stroma containing aggregates, nests, and masses of the specialized glomus cells that typically are arranged around vessels
Typical Outcome	Excision is curative

Vascular Ectasias (benign)	
<i>Etiology</i>	<i>Not a true neoplasm</i> Characterized by localized dilation of preexisting vessels
<i>Morphology</i>	<ul style="list-style-type: none"> • Telangiectasis = congenital anomaly or acquired exaggeration of preformed vessels; composed of prominent capillaries, venules, and arterioles; small focal red lesion, us. in skin or mucous membranes • Nevus flammeus = classic “birthmark” = most common form of ectasia; characteristically forms on head and neck (dilation of vessels in dermis); flat, ranges in color from light pink to deep purple; most fade and regress <ul style="list-style-type: none"> ▪ Port-Wine Stain = special form of nevus flammeus; may grow proportionately w/ child; skin surface thickens; no tendency to fade ▪ Sturge-Weber syndrome = extremely uncommon congenital disorder attributed to faulty development of certain mesodermal and ectodermal elements; characterized by venous angiomatous masses in cortical leptomeninges and by ipsilateral port-wine nevi of the face (trigeminal nerve distribution); often assoc. w/ mental retardation, seizures, hemiplegia, radiopacities in skull • Spider Telangiectasia (Arterial Spider) = non-neoplastic lesion; radial, often pulsatile array of dilated subcutaneous arteries or arterioles about central core that blanches when pressure is applied to its center; us. on face, neck, or upper chest; most frequent in pregnant women and in pts. with cirrhosis (role of estrogen) • ***Osler-Weber-Rendu disease = autosomal dominant; genetic malformations, dilated capillaries and veins; present from birth; distributed widely over skin and mucous membranes of oral cavity, lips, and respiratory, GI, and GU tracts; rupture may occur → serious nosebleeds, bleeding into gut, hematuria

Bacillary Angiomatosis (benign)	
<i>Etiology</i>	<ul style="list-style-type: none"> • Opportunistic infection of immunocompromised persons • Caused by infection with G(-) bacilli of <i>Bartonella</i> family, particularly <i>Bartonella henselae</i> and <i>B. Quintana</i>
<i>Morphology/ Clinical Presentation</i>	<ul style="list-style-type: none"> • One to numerous red papules and nodules or rounded subcutaneous masses • Vascular proliferations clinically resemble tumors and involve skin, bone, brain, and other organs • Histologically: tumor-like growth pattern involving proliferation of capillaries; protuberant epithelioid endothelial cells w/ nuclear atypia and mitoses; numerous stromal neutrophils, nuclear dust, and purplish granular material consisting of causative bacteria
<i>Typical Outcome</i>	Clear infection w/ macrolide antibiotics (erythromycin)
<i>Other</i>	<i>Bacillary peliosis</i> = closely related vascular lesion of the liver and spleen (same etiology)

Kaposi Sarcoma (low grade malignant)	
<i>Epidemiology</i>	<ul style="list-style-type: none"> • Chronic, classic or European KS – 90% occur in older men of Eastern European (especially Ashkenazi Jews) or Mediterranean descent;

	<p>uncommon in US; not assoc. w/ HIV</p> <ul style="list-style-type: none"> • <i>Lymphadenopathic, African or endemic KS</i> – common in portions of Africa; prevalent among young Bantu children of South Africa (same geographic distribution as Burkitt lymphoma)- no skin lesions • Transplant-associated (or <i>immunosuppression-associated</i>) KS – typically occurs several months to few years postoperatively in organ transplant recipients who receive high doses of immunosuppressive therapy • KS is the most common AIDS-associated cancer in the United States – no site of predilection; involvement of lymph nodes and gut and wide dissemination tend to occur early
Pathophysiology	95% of KS lesions are infected with KSHV (HHV-8)
Morphology	<ul style="list-style-type: none"> • 3 stages: patch, plaque, and nodule • Patches = pink to red to purple solitary or multiple macules, us. confined to distal lower extremities or feet; composed of dilated, irregular, angulated blood vessels lined by endothelial cells w/ interspersed infiltrate of lymphocytes, plasma cells, and macrophages (sometimes containing hemosiderin); lesions difficult to distinguish from granulation tissue • Raised plaques = confluence of patches; composed of dermal, dilated, jagged vascular channels lined by plump spindle cells accompanied by perivascular aggregates of similar spindled cells; red cells, hemosiderin-laden macrophages, lymphocytes, and plasma cells scattered btwn channels; pink, hyaline globules found in spindled cells and macrophages; occasional mitotic figures • Nodules = more distinctly neoplastic; may be composed of sheets of plump, proliferating spindle cells, mostly in dermis or subcutaneous tissues <ul style="list-style-type: none"> ▪ Particularly characteristic = scattered small vessels and slit-like spaces often containing rows of red cells and hyalin droplets ▪ Hemorrhage, hemosiderin pigment, lymphocytes, occasional macrophages ▪ Often accompanied by involvement of lymph nodes and of viscera, particularly in African and AIDS-assoc. Dx
Clinical Presentation	<ul style="list-style-type: none"> • Chronic KS – multiple red to purple skin plaques or nodules, primarily on arms or legs, slowly increasing in size and number, spreading to more proximal sites, often becoming confluent <ul style="list-style-type: none"> ▪ Tumors frequently asymptomatic, localized to skin and subcutaneous tissue; locally persistent; erratic course of lapses and remissions • Endemic KS – children present w/ localized or generalized lymphadenopathy; disease is extremely aggressive; skin lesions are sparse • Transplant-assoc. KS – aggressive; involves lymph nodes, mucosa, and visceral organs in ½ of patients; skin lesions may be absent; lesions sometimes regress when immunosuppressive therapy is markedly reduced, but organ or internal involvement is usually fatal

Hemangioendothelioma (low grade malignant)	
Morphology	<ul style="list-style-type: none"> • Wide spectrum of vascular neoplasms • Histologic features and clinical behavior <i>intermediate between the benign, well-differentiated hemangiomas and frankly malignant</i>

	<p><i>angiosarcomas</i></p> <ul style="list-style-type: none"> • <i>Epithelioid hemangioendothelioma</i> = unique vascular tumor occurring around medium-sized and large veins in soft tissue of adults
Typical Outcome	<p>Most are cured by excision Up to 40% recur, 20% to 30% eventually metastasize, perhaps 15% of patients die</p>

Angiosarcoma (malignant)	
Epidemiology	Occur in both sexes, more often in older adults
Pathophysiology	<ul style="list-style-type: none"> • Hepatic angiosarcomas assoc. w/ distinct carcinogens (arsenic, Thorotrast, polyvinyl chloride) • <i>Lymphangiosarcomas</i> arise in setting of lymphedema, most typically ~ 10 years after radical mastectomy for breast cancer
Morphology	<ul style="list-style-type: none"> • Malignant endothelial neoplasms • Small, sharply demarcated, asymptomatic, often multiple red nodules → eventually become large, fleshy masses of pale, gray-white, soft tissue; margins blend w/ surrounding structures • Central softening, areas of necrosis, and hemorrhage are frequent • All degrees of differentiation of these tumors may be found • EC derivation demonstrated by staining for CD31, CD34, or vWF
Clinical Presentation	Occur anywhere in body but most commonly in skin, soft tissue, breast, and liver
Typical Outcome	<ul style="list-style-type: none"> • Local invasion and distal metastatic spread • Majority of patients have poor outcome w/ very few surviving 5 years

The Heart

Normal

- Heart failure = sarcomere lengths are too long due to ventricular dilation → contractility is reduced
- Atrial myocytes – smaller than ventricular myocytes; contain *specific atrial granules* (electron-dense granules, storage of ANP)
 - ANP → vasodilation, diuresis (beneficial in CHF)
- **Ventricular myocytes – produce BNP (in response to ↑ ventricular pressure and volume) and CNP (in response to shear stress)**
- *Intercalated disks* = specialized intercellular junctions permit both mechanical and electrical (ionic) coupling; unique to myocytes
- *Gap junctions* = clusters of plasma membrane channels directly linking cytoplasmic compartments of neighboring cells; facilitate synchronous myocyte contraction (provide electrical coupling w/ relatively unrestricted passage of ions across membranes of adjoining cells)
 - Abnormalities in spatial distribution of gap junctions → arrhythmias
- Coronary arteries – originate from aorta immediately distal to aortic valve in sinuses of Valsalva; *epicardial coronary arteries* and smaller vessels that penetrate myocardium (*intramural arteries*); one capillary per myocytes
 - **Left anterior descending (LAD) – supplies apex, anterior wall of LV, and anterior 2/3 of ventricular septum**
 - **Left circumflex (LCX) – supplies lateral wall of LV; can give rise to posterior descending branch and perfuse posterior 1/3 of septum (left dominant circulation)**

- **Right coronary artery (RCA) – supplies RV free wall & posterobasal wall of LV; can give rise to post. descending branch and perfuse post. 1/3 of septum (right dominant circulation, 80% of pts.)**
- **Collateral circulation = intercoronary anastomoses**
- **Subendocardium (myocardium adjacent to ventricular cavities) = most susceptible to ischemic damage**
- **Semilunar valves = pulmonary and aortic; 3 cusps stretch to 150% normal size to fill orifice during diastole; relaxed and open during systole**
 - *Nodule of Arantius* = small nodule in center of free edge of each cusp to facilitate closing
 - Defects or fenestrations of underneath side of cusps → regurgitation
- **AV valves = tricuspid, mitral; 2 leaflets attached to *cordae tendinae* (direct attachment to papillary muscles and ventricular wall)**
 - LV dilation or ruptured cord or papillary muscle → regurgitation
 - Lined w/ endothelium
 - Layered architecture = dense collagenous core (*fibrosa*) close to outflow surface, continuous w/ valvular supporting structures; mechanical integrity; central core of loose connective tissue (*spongiosa*), shock absorbing; layer rich in elastin (*ventricularis*) below inflow surface
 - Calcific aortic stenosis = nodular calcification beginning in interstitial cells
 - Rheumatic heart disease = fibrotic thickening
- **Age-related changes**
 - Chambers: ↑ LA cavity, ↓ LV cavity, sigmoid-shaped ventricular septum
 - Valves: **aortic valve calcific deposits**, mitral valve annular calcific deposits, fibrous thickening of leaflets, buckling of mitral valve leaflets toward LA, Lambl excrescences (small filiform processes on closure lines of aortic and mitral valves)
 - Coronary arteries: **tortuosity, increased cross-sectional lumen area**, calcific deposits, ATH plaques
 - Myocardium: ↑ mass, ↑ subepicardial fat, brown atrophy, lipofuscin deposition, basophilic degeneration, amyloid deposits
 - Aorta: dilated ascending aorta w/ rightward shift, elongated tortuous thoracic aorta, sinotubular junction calcific deposits, elastic fragmentation, collagen accumulation, ATH plaques

CV dysfunction – 5 principal mechanisms:

Failure of pump = weak contraction or decreased relaxation

Obstruction = increased ventricular pressure and work

Regurgitation = increased ventricular volume and work

Conduction = arrhythmias

Defect in circ system = example: gun shot wound through aorta, permits blood to escape

Congestive Heart Failure	
<i>Etiology</i>	<ul style="list-style-type: none"> • Us. caused by slowly developing intrinsic deficit in myocardial contraction • Most instances are consequence of progressive deterioration of myocardial contractile function (<i>systolic dysfunction</i>) – often occurs w/ ischemic injury, pressure or volume overload, or dilated cardiomyopathy <ul style="list-style-type: none"> ➤ MOST FREQUENT specific causes = ischemic heart disease, HTN • Sometimes results from inability of heart chamber to relax, expand,

	<p>and fill during diastole (diastolic dysfunction) – can occur w/ massive LV hypertrophy, myocardial fibrosis, deposition of amyloid, or constrictive pericarditis</p> <ul style="list-style-type: none"> • Hyperthyroid → cardiac hypertrophy
Pathophysiology	Characterized by ↓ CO (sometimes called forward failure) or damming back of blood in the venous system (so-called backward failure), or both
Morphology	<ul style="list-style-type: none"> • Cardiac hypertrophy – ↑ myocyte size us. accompanied by ↓ capillary density, ↑ intercapillary distance, and deposition of fibrous tissue <ul style="list-style-type: none"> ➢ Concentric hypertrophy results in pressure-overloaded ventricles (HTN, aortic stenosis) → ↑ wall thickness, ↓ cavity diameter ➢ Volume-overload hypertrophy = dilation w/ ↑ ventricular diameter; muscle mass and wall thickness ↑ in proportion to chamber diameter • Left sided heart failure – LV us. dilated and hypertrophied; secondary enlargement of LA can cause atrial fibrillation, compromised SV, stasis, thrombus formation (substantially ↑ risk for embolic stroke) <ul style="list-style-type: none"> ➢ Lungs: pulmonary congestion & edema results from ↑ pressure in pulmonary veins (Kerley B lines on x-ray, “heart failure cells” in lungs) → dyspnea, orthopnea, paroxysmal nocturnal dyspnea, cough ➢ Kidneys: ↓ renal perfusion → activation of renin-AG system → volume expansion → ANP release to balance; azotemia can result if hypoperfusion is severe (prerenal ARF) • Right sided heart failure – rare in isolated form; us. follows LVHF; chronic severe pulmonary HTN → hypertrophy, dilation of RV and RA <ul style="list-style-type: none"> ➢ Lungs: pleural effusions → partial atelectasis ➢ Liver: congestive hepatomegaly (passive congestion), centrilobular necrosis w/ sinusoidal congestion; eventual progression to cirrhosis ➢ Spleen: congestive Splenomegaly w/ marked sinusoidal dilation ➢ Ascites ➢ Kidneys: greater fluid retention, more pronounced azotemia compared to LVHF ➢ Brain: same as LVHF ➢ SubQ tissue: peripheral edema = HALLMARK of Right sided HF <ul style="list-style-type: none"> ▪ Anasarca = generalized massive edema
Other	Most common cause of right sided failure is left sided failure

Congenital heart disease = Trisomy 21 is the MOST COMMON known genetic cause of congenital heart disease- causes endocardial cushion defects; congenital rubella infection also causes congenital heart dx

- Chromosome 22q11.2 deletions = DiGeorge Syndrome, common genetic cause of congenital heart defects
- **Left-to-right shunt** → ↑ pulmonary blood flow → medial hypertrophy and vasoconstriction of pulmonary vessels → RV hypertrophy → RHF

- Eventually pulmonary vascular resistance increases toward systemic levels → shunt reversal to right-to-left → unoxygenated blood in systemic circulation → **late cyanotic congenital heart disease (Eisenmenger syndrome)**
 - Cyanosis develops months or years after birth following shunt reversal
- **Ventricular septal defect (VSD)** is **MOST COMMON** congenital heart disease = incomplete closure of ventricular septum allows free communication from left to right ventricle; frequently assoc. w/ other structural defects such as tetralogy of Fallot; ~ 30% occur as isolated anomalies; **MALES > females**
 - **Membranous VSD = 90%** involve region of membranous septum
 - **Infundibular VSD** = below pulmonary valve
 - Swiss-cheese septum = multiple openings w/in muscular septum
 - Surgical closure of asymptomatic VSDs not attempted during infancy (~ 50% of small muscular VSDs close spontaneously)
 - Surgical correction indicated at age 1 year w/ large defects before obstructive pulmonary vascular disease becomes irreversible
- **Atrial septal defect (ASD)** – abnormal opening in atrial septum (NOT patent foramen ovale) allows free communication from left to right atrium; us. singular and **asymptomatic until adulthood** (4th decade; **FEMALES > males**); murmur often present as result of excessive flow through pulmonary valve; volume hypertrophy of RA and RV develops eventually
 - **Secundum ASD = 90% of all ASDs; defect located at and resulting from deficient or fenestrated oval fossa**
 - **Primum ASD** = 5% of ASDs; occur adjacent to AV valves; us. assoc. w/ cleft anterior mitral leaflet (partial AVSD)
 - **Sinus venosus ASD** = 5% of ASDs; located near entrance of superior vena cava; commonly accompanied by anomalous connections of right pulmonary veins to superior vena cava or RA
 - Surgical closure to reverse hemodynamic abnormalities and prevent complications (incl. HF, **paradoxical embolism**, and irreversible pulmonary vascular disease)
- **Atrioventricular septal defect (AVSD)** – abnormal development of embryologic AV canal, **superior and inferior endocardial cushions fail to fuse adequately** → incomplete closure of AV septum, inadequate formation of tricuspid and mitral valves
 - **Partial AVSD** – consists of primum ASD and cleft anterior mitral leaflet → mitral insufficiency
 - **Complete AVSD** – consists of large combined AV septal defect and large common AV valve (**essentially a hole in the center of the heart** → **all 4 chambers freely communicate**)
 - **> 1/3 of all complete AVSD pts. have Down syndrome**
- **Patent ductus arteriosis (PDA)** – 90% occur as isolated anomalies; rest are most often assoc. w/ VSD, coarctation of aorta, or pulmonary or aortic Stenosis; **continuous “machinery-like” murmur**
 - Isolated PDA should be closed as early in life as is feasible
 - ****Preservation of ductal patency (by administering prostaglandin E)** important for survival of infants w/ obstructed pulmonary or systemic blood flow
- **Right-to-left shunt** → cyanosis early in postnatal life due to poorly oxygenated blood entering systemic circulation; assoc. w/ **paradoxical embolism (bland or septic emboli arising in peripheral veins bypass lungs and directly enter systemic circulation)**, **clubbing of finger tips and toes** (hypertrophic osteoarthropathy) and polycythemia

- **Transposition of great arteries (TGA)** – DIABETIC MOTHER; aorta arises from RV; pulmonary artery emanates from LV—cyanosis minutes after birth
 - Incompatible with postnatal life unless a shunt exists for adequate mixing of blood – reason for wanting to keep PDA open
 - Without surgery, most patients die w/in first months of life
- **Tetralogy of Fallot** – MOST COMMON cyanotic congenital heart dx; due to developmental errors in mesenchymal tissue migration (anterosuperior displacement of the infundibular septum); pt. often assumes squatting position to relieve symptoms
 - 4 features = VSD, obstruction to RV outflow tract (narrowing of infundibulum, subpulmonary stenosis), aorta that overrides the VSD (aortic inlet spans both ventricles), RV hypertrophy (→ “boot shaped” heart)
 - ***Clinical consequences depend primarily on severity of subpulmonary Stenosis
 - If subpulmonary stenosis is mild → abnormality resembles isolated VSD, shunt may be left-to-right w/out cyanosis (= pink tetralogy)
 - As obstruction increases in severity → greater resistance to RV outflow approaching level of systemic vascular resistance → right-to-left shunting predominates → cyanosis (classic tetralogy of Fallot)
- **Truncus arteriosus** – developmental errors in mesenchymal tissue migration; embryologic truncus arteriosus does not separate into aorta and pulmonary artery → single great artery receives blood from both ventricles, gives rise to the systemic, pulmonary, and coronary circulations.
 - Accompanied by underlying VSD → blood from right and left ventricles mixes → early systemic cyanosis, ↑ pulmonary blood flow → danger of irreversible pulmonary HTN
- **Total anomalous pulmonary venous connection (TAPVC)** – no pulmonary veins directly join LA; results embryologically when common pulmonary vein fails to develop or becomes atretic → primitive systemic venous channels from lungs remain patent
 - Either patent foramen ovale or ASD is always present (allows pulmonary venous blood to enter LA)
 - RA, RV, pulmonary trunk are dilated
 - LA hypoplastic, LV normal
- **Tricuspid atresia** – complete occlusion of tricuspid valve orifice results embryologically from unequal division of AV canal → mitral valve is larger than normal
 - Almost always assoc. w/ hypoplasia of RV
 - need an ASD and PDA to get flow to lungs
- **Obstruction** → obstructions to flow because of abnormal narrowing of chambers, valves, or blood vessels
 - **Pulmonary Stenosis** – pulmonary valve obstruction, can be assoc. w/ tetralogy of Fallot or TGA
 - Right ventricular hypertrophy often develops
 - **Coarctation of aorta** – MALES > females (2:1) but common in Turner syndrome
 - **Infantile form:** tubular hypoplasia of aortic arch proximal to a PDA;

- **Adult form:** Coarctation w/out PDA – **HTN in upper extremities, weak pulses and lower bp in lower extremities**; assoc. w/ manifestations of arterial insufficiency (claudication, coldness); discrete ridge-like infolding of aorta, just opposite closed ductus arteriosus (ligamentum arteriosum) distal to arch vessels; radiographically visible **rib-notching, cyanosis in lower half of body**
- **Aortic Stenosis** – prominent **systolic murmur**; pressure hypertrophy of the LV develops
 - **Hypoplastic left heart syndrome** = severe congenital aortic stenosis or atresia → obstruction of LV outflow tract → **hypoplasia of LV** and ascending aorta; dense, **porcelain-like left ventricular endocardial fibroelastosis**
 - **Supravalvular aortic stenosis** = inherited form of aortic dysplasia in which ascending aortic wall is greatly thickened, causing luminal constriction; may be related to developmental disorder affecting multiple organ systems, including vascular system, **which includes hypercalcemia of infancy (Williams syndrome)**; assoc. w/ **mutations in elastin gene**

Ischemic Heart Disease (IHD), sometimes called Coronary Artery Disease (CAD)

- **Ischemia** = inadequate oxygen and nutrient supply + inadequate metabolite removal
- 4 syndromes:
 - **Myocardial infarction (MI)** = **MOST IMPORTANT form of IHD**; duration and severity of ischemia causes death of heart muscle; acute plaque change induces total thrombotic occlusion; same risk factors as ATH; **LEADING CAUSE OF DEATH** in the US and industrialized nations; Blacks = whites; **MEN > women** (until old age, then *men = women*)
 - **Angina pectoris** = ischemia is less severe and does not cause death of cardiac muscle
 - **Def:** Paroxysmal, us. recurrent attacks of substernal or precordial chest discomfort (variously described as constricting, squeezing, choking, or knifelike) caused by transient (15 seconds to 15 minutes) myocardial ischemia that falls short of inducing the cellular necrosis that defines infarction
 - **Stable angina** – results from **↑ myocardial oxygen demand** that outstrips ability of stenosed coronary arteries to **↑ O₂ delivery**; **not assoc. w/ plaque disruption**; **us. relieved by rest (thereby decreasing demand) or nitroglycerin (vasodilator)** – *typically subendocardial ischemia- ST depression on EKG*
 - **Prinzmetal angina** – caused by **coronary artery spasm**; uncommon pattern of episodic angina **unrelated to physical activity, HR, or bp**; EKG shows **elevated ST, indicative of transmural ischemia**; generally responds promptly to vasodilators (nitroglycerin, calcium channel blockers)
 - **Unstable angina** = **most threatening**; sudden change in plaque morphology → partially occlusive platelet aggregation or mural thrombus, vasoconstriction → severe but transient reductions in coronary blood flow
 - *****Often the prodrome of subsequent acute MI**
 - **Chronic IHD** w/ HF

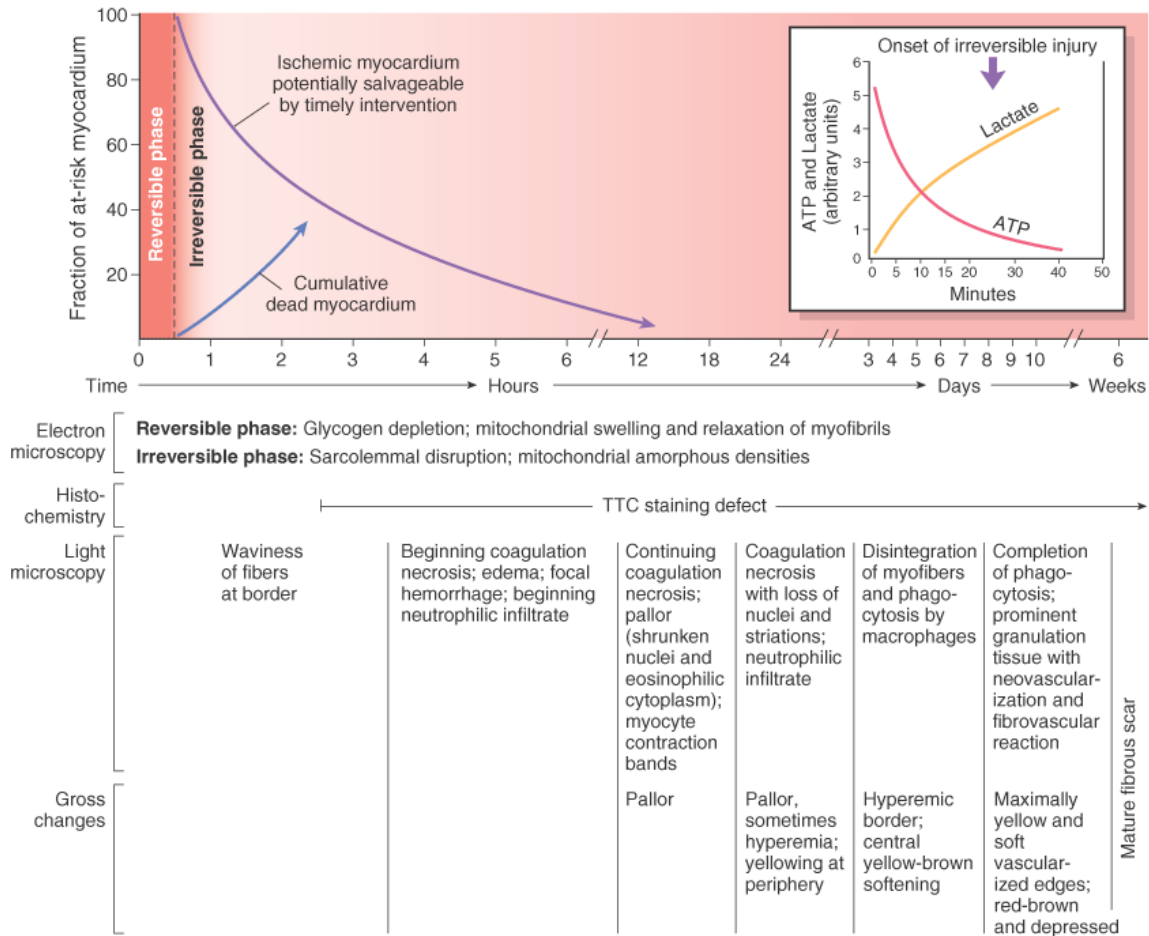
- **Sudden cardiac death** – frequently involves coronary lesion w/ plaque and often partial thrombus and possibly embolus → regional myocardial ischemia → **fatal ventricular arrhythmia**
- **Pathogenesis** – diminished coronary perfusion relative to myocardial demand → ischemia
 - **Fixed obstructive lesion ≥ 75% generally causes symptomatic ischemia induced by exercise**
 - **90% stenosis → inadequate coronary blood flow even at rest**
 - **Acute Coronary Syndromes = Acute MI, sudden cardiac death, and unstable angina**
 - **initiated by unpredictable and abrupt conversion of stable atherosclerotic plaque to unstable and potentially life-threatening atherothrombotic lesion through superficial erosion,**
 - Plaque disruption, platelet aggregation and intraluminal thrombosis are common, repetitive, often clinically silent complications of atheroma
 - Coronary Thrombus – results in occlusion of coronary vessels → MI
 - Vasoconstriction due to circulating adrenergic agonists, locally released platelet contents, atheroma-assoc. endothelial dysfunction → compromised lumen size → increased mechanical forces → plaque disruption

Myocardial Infarction	
<i>Etiology</i>	<ul style="list-style-type: none"> • 90% of transmural MIs due to sudden ATH plaque change → platelet aggregation, activation → vasospasm → thrombus occlusion of coronary vessel
<i>Pathophysiology</i>	<ul style="list-style-type: none"> • Potentially reversible myocardial responses to ischemia: <ul style="list-style-type: none"> ➤ Cessation of aerobic glycolysis, initiation of anaerobic glycolysis w/in seconds → inadequate production of ATP, accumulation of noxious breakdown products (lactic acid) → loss of contractility can occur w/in 60 sec → loss of 50% of ATP w/in 10 min → acute heart failure before myocytes even die ➤ Ultrastructural changes (myofibrillar relaxation, glycogen depletion, cell and mitochondrial swelling) develop w/in few minutes • Severe ischemia lasting ≥ 20-40 minutes → sarcolemma disruption, loss of up to 90% of ATP → irreversible damage & death of myocytes (coagulative necrosis begins in subendocardium, moves as a wavefront through ventricular wall)
<i>Morphology</i>	<ul style="list-style-type: none"> • Transmural infarcts – ischemic necrosis involves full or nearly full thickness of ventricular wall; most MIs are this type; most involve at least a portion of LV wall and ventricular septum • Subendocardial infarct – ischemic necrosis limited to inner 1/3-1/2 of ventricular wall; subendocardial zone is least well-perfused region of myocardium → most vulnerable to ischemia • Typical right dominant heart <ul style="list-style-type: none"> ➤ LAD (40-50%) – infarct involves anterior wall of LV near apex; anterior portion of ventricular septum; apex circumferentially ➤ Right coronary artery (30% to 40%) – infarct involves inferior/posterior wall of LV; posterior portion of ventricular septum; inferior/posterior RV free wall in some cases ➤ Left circumflex coronary artery (15% to 20%) – infarct involves lateral wall of LV except at apex

	<p>Evolution of Morphologic Changes in Myocardial Infarction (MUST KNOW ALL OF THIS!!)</p> <ul style="list-style-type: none"> • 0-½ hrs: relaxation of myofibrils (wavy); glycogen loss; mitochondrial swelling • ½-4 hrs: Sarcolemmal disruption, mitochondrial amorphous densities • 4-12 hrs: occasional dark mottling, beginning coagulation necrosis, edema, hemorrhage • 12-24 hrs: dark mottling; ongoing coagulation necrosis, pyknosis of nuclei, myocyte hypereosinophilia, marginal contraction band necrosis, beginning neutrophilic infiltrate • 1-3 days: mottling w/ yellow/tan infarct center, coagulation necrosis w/ loss of nuclei and striations, interstitial infiltrate of neutrophils • 3-7 days: hyperemic border; beginning disintegration of dead myofibers w/ 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 wks: Gray-white scar, progressive from border toward core of infarct (most healed at periphery); Increased collagen deposition, with decreased cellularity • > 2 mo: Dense collagenous scar
<p>Morphology (con't)</p>	<p>Repetitive necrosis of adjacent regions → progressive extension of individual infarct over period of days to weeks (most healed portion is in the center)</p> <ul style="list-style-type: none"> • Subendocardial infarcts tend to be smaller than transmural • Reperfused heart → hemorrhagic b/c damaged vessels are leaky; myocytes already irreversibly injured at time of reflow often have <i>necrosis w/ contraction bands</i> (= intensely eosinophilic transverse bands composed of closely packed hypercontracted sarcomeres due to exposure to high concentration of Ca²⁺ ions from plasma) <ul style="list-style-type: none"> ➢ Reperfusion injury = generation of oxygen free radicals from infiltrating leukocytes during reperfusion → causes hemorrhage and endothelial swelling → occlusion → no local reperfusion • Hibernation = myocardium subjected to persistently low flow → chronically depressed function, may undergo profound restoration
<p>Clinical Course</p>	<ul style="list-style-type: none"> • Pts. present w/ tachycardia, weak pulses, diaphoresis, Dyspnea, EKG changes • <i>Preferred biomarkers for myocardial damage are cardiac-specific proteins, particularly Troponin-I (TnI) and Troponin-T</i>. Troponins regulate calcium-mediated contraction of cardiac and skeletal muscle; have nearly complete tissue specificity and high sensitivity; are not normally detectable in circulation; after acute MI, levels rise at 2-4 hours and peak at 48 hours; remain elevated for 7-10 days after acute event • Cardiac creatine kinase (CK-MB) remains best alternative to troponin measurement; CK-MB activity begins to rise within 2 to 4 hours of onset of MI, peaks at about 24 hours, and returns to normal w/in approx. 72 hours • Serum CRP: levels > 3 mg/L assoc. w/ highest risk of CV disease; levels of 1-3 mg/L assoc. w/ moderate risk

	<ul style="list-style-type: none"> • Myocardial infarcts less than 12 hours old are usually not apparent on gross examination (autopsy)
<p><i>Typical Outcome</i></p>	<ul style="list-style-type: none"> • ½ of deaths assoc. w/ acute MI occur w/in 1 hour of onset; these individuals never reach the hospital • Factors assoc. w/ poor prognosis = advanced age, female gender, diabetes mellitus, and previous MI • Most effective way to salvage ischemic myocardium threatened by infarction = restore tissue perfusion ASAP; early reperfusion → limit infarct size <ul style="list-style-type: none"> ➢ Thrombolysis – removes thrombus ➢ Balloon angioplasty (a.k.a. percutaneous transluminal coronary angioplasty, or PTCA) – removes thrombus and underlying plaques ➢ Coronary arterial bypass graft (CABG) – provides flow around obstructed vessel • Large transmural infarcts → higher probability of cardiogenic shock, arrhythmias, and late CHF <ul style="list-style-type: none"> ➢ <i>Contractile dysfunction</i> = Cardiogenic shock, severe pump failure ➢ Arrhythmias = MOST COMMON CONSEQUENCE = conduction disturbances and myocardial irritability (sinus bradycardia, heart block, tachycardia, ventricular premature contractions or ventricular tachycardia, ventricular fibrillation) ➢ <i>Progressive late heart failure</i> = chronic ischemic heart disease • Anterior transmural infarcts → greatest risk for free-wall rupture, expansion, mural thrombi, and aneurysm (anterior infarcts have a substantially worse clinical course than those with inferior/posterior infarcts) <ul style="list-style-type: none"> ➢ <i>Myocardial rupture</i> (free wall) → hemopericardium → cardiac tamponade → death <ul style="list-style-type: none"> ▪ Lateral wall at midventricular level = most common site for post-MI free-wall rupture ▪ Risk factors = age > 60, female gender, pre-existing HTN, and lack of LVH ➢ <i>Myocardial rupture</i> (septum) → left-to-right shunt ➢ <i>Papillary muscle dysfunction</i> → acute onset of severe mitral regurge ➢ <i>Infarct expansion</i> = disproportionate stretching, thinning, and dilation of infarct region; often assoc. w/ mural thrombus ➢ <i>Mural thrombus</i> = due to stasis w/in ventricle ➢ Ventricular aneurysm = large region of thin scar tissue, bulges during systole • Posterior transmural infarcts → more likely to be complicated by serious conduction blocks, right ventricular involvement, or both <ul style="list-style-type: none"> ➢ <i>RV infarction</i> – often accompanies ischemic injury of adjacent posterior LV and ventricular septum • Pericarditis – occurs 2-4 days after transmural MI; us. resolves over time

Figure 12-17 Temporal sequence of early biochemical, ultrastructural, histochemical, and histologic findings after onset of severe myocardial ischemia.*** KNOW THIS FIGURE!!



Markers of Myocardial Injury

Emerging cardiac markers:

- Troponins – ***troponin I and troponin T*** – Because troponin is detected using monoclonal antibody-based immunoassays, the presence of unusual antibodies, such as persons with rheumatoid arthritis, those employed as veterinarians, or those who have received monoclonal antibody drug therapy, may produce false-positives as well as false negatives
 - Troponin I inhibits muscle contraction when calcium is not present. Troponin T connects the troponin complex to tropomyosin.
 - ***Cardiac specific troponins I (cTnI) and T (cTnT)*** – different a.a. sequence than skeletal muscle counterpart – **higher specificity and higher sensitivity than CK-MB**
 - Troponin-C binds calcium. (same in skeletal and cardiac muscle)
- ***C-reactive protein (CRP)*** – nonspecific response by liver to inflammation, infection, tissue damage; **predictive of coronary disease and CHF**
- ***Brain natriuretic peptide (BNP)*** – released from ventricles in response to increased ventricular wall tension; causes vasodilation, venodilation, increased renal blood flow

Marker	Earliest Rise	Peak	Return to Normal	Abnormal Value*
Total CK	3-6 hrs	24-36 hrs	3 days	150-180 u/L

CK-MB >3% of total	4-8 hrs	12-24 hrs	3-4 days	>10 µg/mL or
Myoglobin	1-3 hrs	6-9 hrs	12 hrs	
CTnT	3-4 hrs	10-24 hrs	1-3 wks	>0.1 µg/mL
CtnI	3-4 hrs	10-24 hrs	1-3 wks	>1.5 µg/L

Ischemic Cardiomyopathy, Chronic IHD	
Etiology	<ul style="list-style-type: none"> • <i>Postinfarction cardiac decompensation owing to exhaustion of compensatory hypertrophy of non-infarcted viable myocardium that is itself in jeopardy of ischemic injury</i> → progressive heart failure develops as consequence of ischemic myocardial damage
Epidemiology	~ 1/2 of cardiac transplant pts.
Morphology	<ul style="list-style-type: none"> • Large, heavy hearts secondary to LVH and dilation • Moderate to severe stenosing atherosclerosis of coronary arteries • Discrete, gray-white scars of healed infarcts are usually present • Major microscopic findings = myocardial hypertrophy, diffuse subendocardial vacuolization, scars of previously healed infarcts
Clinical Presentation	Diagnosis made by insidious onset of CHF in patients who have had past episodes of MI or anginal attacks

Sudden Cardiac Death	
Etiology	Unexpected death from cardiac causes early after symptom onset (us. w/in 1 hour) or w/out onset of symptoms
Pathophysiology	<ul style="list-style-type: none"> • <i>Ultimate mechanism of SCD is most often a lethal arrhythmia</i> • Romano-Ward Syndrome = autosomal dominant long QT syndrome, causes heightened cardiac excitability and episodic ventricular arrhythmias
Morphology	<ul style="list-style-type: none"> • 80-90% have marked coronary atherosclerosis w/ critical (>75%) stenosis involving at least 1 of the 3 major vessels • Subendocardial myocyte vacuolization indicative of severe chronic ischemia is common
Typical Outcome	Prognosis markedly improved by implantation of automatic cardioverter defibrillator (senses and electrically counteracts episodes of ventricular fibrillation)

Systemic (Left-sided) Hypertensive Heart Disease	
Etiology	<ul style="list-style-type: none"> • Response of heart to increased demands induced by systemic HTN
Pathophysiology	<ul style="list-style-type: none"> • HTN induces LV pressure overload hypertrophy w/out dilation of LV • ↑ thickness of LV wall → ↓ compliance → impaired diastolic filling → LA enlargement
Morphology	<ul style="list-style-type: none"> • Microscopically, ↑ transverse diameter of myocytes • Advanced stages → cellular and nuclear enlargement more irregular, variation in cell size among adjacent cells, interstitial fibrosis
Clinical Presentation	<ul style="list-style-type: none"> • Comes to attention by onset of atrial fibrillation (owing to LA

	<p>enlargement) or CHF w/ cardiac dilation, or both</p> <ul style="list-style-type: none"> Minimal criteria for diagnosis of systemic HHD = (1) LVH, us. concentric, in absence of other CV pathology that might have induced it; and (2) Hx or pathologic evidence of HTN
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Pulmonary (Right-sided) Hypertensive Heart Disease (cor pulmonale)	
Etiology	<ul style="list-style-type: none"> <i>Acute cor pulmonale</i> can follow massive pulmonary embolism <i>Chronic cor pulmonale</i> usually implies RVH and dilation secondary to prolonged pressure overload caused by obstruction of pulmonary arteries or arterioles or compression or obliteration of septal capillaries (e.g., owing to primary pulmonary HTN or emphysema)
Morphology	<ul style="list-style-type: none"> <i>Acute cor pulmonale</i> – marked dilation of RV w/out hypertrophy <i>Chronic cor pulmonale</i> – RVH (may even approximate that of LV); sometimes there is secondary compression of LV chamber or tricuspid regurgitation w/ fibrous thickening of tricuspid valve

Valvular Heart Disease

- Stenosis = failure of valve to open completely; impedes forward flow
 - ***Aortic stenosis is the most common of all valvular abnormalities***
- Most frequent causes of the major functional valvular lesions:
 - Aortic stenosis: calcification of anatomically normal and congenitally bicuspid aortic valves
 - Aortic insufficiency: dilation of the ascending aorta, related to hypertension and aging
 - Mitral stenosis: rheumatic heart disease
 - Mitral insufficiency: myxomatous degeneration (mitral valve prolapse)

Calcific aortic stenosis	
Etiology	<i>Acquired aortic stenosis</i> = progressive and advanced age-associated "wear and tear" of either previously anatomically normal aortic valves or congenitally bicuspid valves
Epidemiology	Bicuspid aortic valves ~ 1.4% of live births → predisposition to progressive degenerative calcific aortic stenosis
Pathophysiology	Functional valve area decreased sufficiently → measurable obstruction to outflow → left ventricular myocardium pressure overload → LVH → myocardial ischemia → angina pectoris
Morphology	<ul style="list-style-type: none"> Hallmark = heaped-up calcified masses w/in aortic cusps that ultimately protrude through outflow surfaces into sinuses of Valsalva, preventing opening of cusps
Clinical Presentation	<ul style="list-style-type: none"> Pts. present in 6th-7th decades w/ congenitally bicuspid valves but not until 8th-9th decades w/ previously normal valves Systolic and diastolic myocardial dysfunction w/ symptoms of CHF
Typical Outcome	<ul style="list-style-type: none"> Onset of angina, CHF, or syncope → poor prognosis

Mitral Annular Calcification = irregular, stony hard, and occasionally ulcerated nodules (2–5 mm thick) that lie behind leaflets; generally does not affect valvular function

- **Most common in women > 60 and individuals w/ myxomatous mitral valve or elevated left ventricular pressure**
- Can lead either to regurgitation by interfering with systolic contraction of the mitral valve ring, to stenosis by impairing opening of the mitral leaflets, or to arrhythmias and occasionally sudden death by the calcium deposits penetrating sufficiently deeply to impinge on AV conduction system
- May provide a site for thrombi that can embolize → increased risk of stroke
- **Can also be the nidus for infective endocarditis**

Myxomatous Mitral Valve (Mitral Valve Prolapse, MVP)	
<i>Epidemiology</i>	Most often young women
<i>Pathophysiology</i>	Might be assoc. w/ connective tissue diseases (common in Marfan syndrome) → poor collagen cross-linking
<i>Morphology</i>	<ul style="list-style-type: none"> • Intercordal ballooning (hooding) of the mitral leaflets • Tendinous cords are elongated, thinned, and occasionally ruptured • Histologically = attenuation of fibrosa layer of valve, focally marked thickening of spongiosa layer w/ deposition of mucoid (myxomatous) material
<i>Clinical Presentation</i>	Presence of midsystolic click <ul style="list-style-type: none"> • May have CP, Dyspnea, fatigue, psychiatric manifestations (anxiety)
<i>Typical Outcome</i>	<ul style="list-style-type: none"> • 4 serious complications = infective endocarditis, mitral insufficiency, stroke or other systemic infarct, arrhythmias

Rheumatic Heart Disease	
<i>Epidemiology</i>	<ul style="list-style-type: none"> • RHD is most common in children ages 5-15 • RHD is overwhelmingly the most frequent cause of mitral stenosis (99% of cases)
<i>Pathophysiology</i>	<ul style="list-style-type: none"> • Acute rheumatic fever = hypersensitivity reaction induced by group A streptococci • Chronic valvular deformities, characterized principally by deforming fibrotic valvular disease (particularly mitral stenosis) → permanent dysfunction and severe, sometimes fatal, cardiac problems decades later • Tight mitral Stenosis → LA progressively dilates, may harbor mural thrombus either in appendage or along wall
<i>Morphology</i>	<ul style="list-style-type: none"> • Aschoff bodies = foci of swollen eosinophilic collagen surrounded by lymphocytes (primarily T cells), occasional plasma cells, and plump macrophages called Anitschkow cells (pathognomonic for RF) • Acute RF – pancarditis; diffuse inflammation, Aschoff bodies found in any of 3 layers of heart (pericardium, myocardium, or endocardium) <ul style="list-style-type: none"> ➢ “Bread and butter” pericarditis ➢ ***MacCallum plaques = irregular thickenings in LA subendocardium • Chronic RF – mitral (or tricuspid) valve shows leaflet thickening, commissural fusion and shortening, and thickening and fusion of tendinous cords; diffuse fibrosis and often neovascularization that obliterate the originally layered and avascular leaflet architecture
<i>Clinical Presentation</i>	<ul style="list-style-type: none"> • Major manifestations = migratory polyarthritis of large joints, carditis, subcutaneous nodules, erythema marginatum of skin, and

	<p>Sydenham chorea (neurologic disorder with involuntary purposeless, rapid movements)</p> <ul style="list-style-type: none"> • Increased vulnerability to reactivation of the disease with subsequent pharyngeal infections
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NonBacterial Thrombotic Endocarditis (NBTE)	
Etiology	<ul style="list-style-type: none"> • Deposition of small masses of fibrin, platelets, and other blood components on leaflets of cardiac valves – vegetations are sterile, do not contain microorganisms • Predisposing conditions: endocardial trauma (indwelling catheter)
Epidemiology	Often encountered in debilitated patients (cancer or sepsis) → previously used term <i>marantic endocarditis</i>
Pathophysiology	<ul style="list-style-type: none"> • Frequently occurs w/ venous thromboses or pulmonary embolism → suggests a common origin in hypercoagulable state w/ systemic activation of blood coagulation such as DIC • May be related to some underlying disease, such as a cancer, esp. mucinous adenocarcinomas of the pancreas <ul style="list-style-type: none"> ➢ Procoagulant effect of circulating mucin, so NBTE can be a part of Trousseau syndrome • Also seen in assoc. w/ nonmucin-producing malignancy (acute promyelocytic leukemia) and in other debilitating diseases or conditions (hyperestrogenic states, extensive burns, sepsis) promoting hypercoagulability
Morphology	Sterile, nondestructive, small (1 to 5 mm) lesions, occur singly or multiply along line of closure of leaflets or cusps
Clinical Presentation	Clinical significance – can produce emboli and resultant infarcts in brain, heart, or elsewhere

Infective Endocarditis (IE)	
Etiology	<ul style="list-style-type: none"> • Colonization or invasion of heart valves or mural endocardium by microbes → formation of bulky, friable vegetations composed of thrombotic debris and organisms, often assoc. w/ destruction of underlying cardiac tissues • Although fungi, rickettsiae (Q fever), and chlamydiae have been responsible, most cases are bacterial (<i>bacterial endocarditis</i>) <ul style="list-style-type: none"> ➢ 50-60% of cases = <i>Streptococcus viridans</i> (think of patient that just had dental work) ➢ 10-20% of cases = <i>Staph aureus</i> (common in i.v. drug users-tricuspid) ➢ Remaining bacteria = enterococci & HACEK group (<i>Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella</i>), all commensals in the oral cavity ➢ Prosthetic valve endocarditis = most commonly coag(-) staphylococci (e.g., <i>S. epidermidis</i>) • Conditions which predispose to IE = seeding of the blood with microbes (most important); valvular deformities such as myxomatous mitral valve, degenerative calcific valvular stenosis, bicuspid aortic valve (calcified or no), and artificial (prosthetic) valves; RHD used to be (not so much anymore); neutropenia, immunodeficiency, malignancy,

	therapeutic immunosuppression, diabetes mellitus, and alcohol or intravenous drug abuse
Pathophysiology	<ul style="list-style-type: none"> • Acute endocarditis = destructive, tumultuous infection, us. of a previously normal heart valve, w/ highly virulent organism → > 50% result in death w/in days-weeks despite antibiotics and surgery • Subacute endocarditis = organisms of low virulence cause infection in previously abnormal heart, esp. on deformed valves → disease may appear insidiously and, even untreated, go away in weeks-months; most pts. recover w/ appropriate antibiotic therapy • Systemic emboli may cause infarcts in brain, kidneys, myocardium, and other tissues → septic infarcts contain organisms
Morphology	<ul style="list-style-type: none"> • Acute – necrotizing, ulcerative, invasive valvular infections <ul style="list-style-type: none"> ➢ Aortic & mitral valves most common sites of infection; right heart valves involved more w/ i.v. drug users ➢ Ring abscess = erosion into underlying myocardium • Fungal endocarditis = larger vegetations than bacterial infection • Subacute – lesions have granulation tissue at base (suggesting chronicity) → fibrosis, calcification, and chronic inflammatory infiltrate may develop over time
Clinical Presentation	<ul style="list-style-type: none"> • Fever is the most consistent sign of IE • Acute – rapidly developing fever, chills, weakness, lassitude • Subacute – nonspecific fatigue, loss of weight, flu-like syndrome • Murmurs present in 90% of patients w/ left-sided lesions • Duke Criteria (standardized assessment of pts. w/ suspected IE) = presence of microorganisms, histological verification of valvular lesion, positive blood culture, echocardiogram, new valvular regurge, predisposing heart lesion, fever, vascular lesions (reflecting microemboli), immunologic phenomenon • Immunologic phenomenon = glomerulonephritis due to trapping of Ag-Ab complexes → hematuria, albuminuria, renal failure; also subcutaneous nodules in pulp of digits (Osler nodes), retinal hemorrhages (Roth spots) due to shortened clinical course of disease w/ antibiotic therapy, rheumatoid factor • Clinical findings secondary to microemboli = petechiae; red, linear, or flame-shaped streaks in the nail bed of the digits (splinter or subungual hemorrhages); erythematous or hemorrhagic nontender lesions on palms or soles (Janeway lesions); septic infarcts; Mycotic aneurysm
Other	Prophylactic use of antibiotics in pts. w/ some form of cardiac anomaly or artificial valve who is having dental, surgical, or other invasive procedure

Libman-Sacks Endocarditis	
Etiology	Mitral and tricuspid valvulitis w/ small, sterile vegetations assoc. w/ SLE
Morphology	<ul style="list-style-type: none"> • Small single or multiple, sterile, granular pink vegetations ranging from 1-4 mm in diameter • Lesions may be on undersurfaces of AV valves, on valvular endocardium, on cords, or on mural endocardium of atria or ventricles • Histologically – lesions contain finely granular, fibrinous eosinophilic material that may contain hematoxylin bodies
Other	***Circulating antiphospholipid antibodies also commonly assoc. w/ venous or arterial thrombosis, recurrent pregnancy loss, or

	thrombocytopenia
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Carcinoid Heart Disease	
<i>Etiology</i>	<ul style="list-style-type: none"> • Cardiac manifestation of systemic syndrome caused by carcinoid tumors; involves endocardium and valves of RH <ul style="list-style-type: none"> ➢ Carcinoid syndrome = episodic flushing of skin, cramps, nausea, vomiting, and diarrhea
<i>Pathophysiology</i>	<ul style="list-style-type: none"> • ***Mostly right sided b/c serotonin and bradykinin are inactivated during passage through the lungs by the monoamine oxidase present in the pulmonary vascular endothelium → not much chance to get to left side of heart • Left-sided lesions can occur when blood containing responsible mediator enters LH due to incomplete inactivation b/c of very high blood levels
<i>Morphology</i>	<ul style="list-style-type: none"> • Distinctive lesions consist of fibrous intimal thickenings on inside surfaces of cardiac chambers and valvular leaflets; located mainly in RV, tricuspid and pulmonic valves, and occasionally in major blood vessels • Endocardial plaquelike thickenings composed predominantly of SMCs and sparse collagen fibers embedded in acid mucopolysaccharide-rich matrix material; underlying structures are intact, incl. valve layers and subendocardial elastic tissue layer
<i>Clinical Presentation</i>	<ul style="list-style-type: none"> • Clinical and pathologic findings relate to elaboration by carcinoid tumors of a variety of bioactive products = serotonin (5-hydroxytryptamine), kallikrein, bradykinin, histamine, prostaglandins, and tachykinins • Plasma levels of serotonin and urinary excretion of serotonin metabolite 5-hydroxyindoleacetic acid correlate w/ severity of RH lesions

Artificial Valves

- 1) *mechanical prostheses* using different types of rigid, mobile occluders composed of nonphysiologic biomaterials
- 2) *tissue valves*, usually *bioprostheses* consisting of chemically treated animal tissue, especially porcine aortic valve tissue, which has been preserved in a dilute glutaraldehyde solution and subsequently mounted on a prosthetic frame

60% of substitute valve recipients develop a serious prosthesis-related problem within 10 years postoperatively

- 1) **Thromboembolic complications** = local obstruction of prosthesis by thrombus or distant thromboemboli; **major problem w/ mechanical valves**; pts. receive long-term anticoag meds
- 2) **Infective endocarditis** = rare complication; major organisms causing such infections are staphylococcal skin contaminants (e.g., *S. aureus*, *S. epidermidis*), streptococci, and fungi
- 3) **Structural deterioration** = uncommon cause of failure of mechanical valves; **MAJOR failure mode of bioprostheses**, w/ calcification and/or tearing causing secondary regurgitation
- 4) Other = hemolysis induced by high blood shear, mechanical obstruction to flow inherent in all artificial valves, inadequate or exuberant healing causing a paravalvular leak or overgrowth of fibrous tissue

Cardiomyopathies = disease whose cause is intrinsic to myocardium

- 25% to 35% of individuals with DCM have a familial (genetic) form
- *Assoc. w/ infections* – **viruses (coxsackie B), Chlamydia, Rickettsia, etc.**
- *Assoc. w/ toxins* – **EtOH, cobalt, catecholamines, CO, lithium, hydrocarbons, arsenic, cyclophosphamide**
 - *Pheochromocytoma* → catecholamine effect → Foci of myocardial necrosis with contraction bands
 - *Anthracycline* chemotherapeutic agents **doxorubicin (Adriamycin) and daunorubicin are well-recognized causes of toxic myocardial injury that can cause DCM – dose-dependent; attributed primarily to lipid peroxidation of myocyte membranes**
 - *Cyclophosphamide* – severe cardiomyopathy may occur following single **high-dose therapy; vascular hemorrhage**
- *Assoc. w/ metabolic disorders* – hypothyroid, hyperthyroid, hypokalemia, hyperkalemia, hemochromatosis, nutritional deficiencies
 - *Hyperthyroid* – tachycardia, palpitations, and cardiomegaly are common
 - *Hypothyroid* – ↓ CO, ↓ SV, ↓ HR, ↑ PVR, ↓ blood volume → narrowing of pulse pressure, prolongation of circulation time, decreased flow to peripheral tissues → characteristic cold sensitivity
 - *Myxedema heart* = **flabby, enlarged, and dilated due to myofiber swelling w/ loss of striations and basophilic degeneration, accompanied by interstitial mucopolysaccharide-rich edema fluid**
 - *Hemochromatosis* = **iron overload, big heart w/ rust-brown color more prominent in ventricles, marked accumulation of hemosiderin in myocytes**
- *Assoc. w/ storage disorders* – Hunter-Hurler syndrome, glycogen storage disease, Fabry disease, amyloidosis
 - Senile cardiac *amyloidosis* (SCA), systemic senile amyloidosis with cardiac involvement, isolated atrial amyloidosis – protein deposits derive from **transthyretin; classic apple-green birefringence demonstrated by polarization of tissue sections stained with Congo red or by the sulfated Alcian blue stain**
 - Autosomal dominant familial transthyretin amyloidosis = 4% of African Americans have gene mutation w/ isoleucine substituted for valine at position 122 (Ile 122) → amyloidogenic/fibrillogenic form of transthyretin
- *Assoc. w/ infiltrative disorders* – **leukemia, carcinomatosis, sarcoidosis, radiation-induced fibrosis**

Hypertrophic cardiomyopathy	
Etiology	Impairment of compliance (diastolic dysfunction) w/ myocardial hypertrophy and intermittent ventricular outflow obstruction (~ 30%)
Pathophysiology	<ul style="list-style-type: none"> • Causes – Genetic; Friedreich ataxia; storage diseases; infants of DIABETIC MOTHERS <ul style="list-style-type: none"> ➢ Mutation in sarcomere proteins (12 identified so far); most cases are familial w/ autosomal dominant transmission (variable expression) ➢ ***Mutations in the β-MHC (β-myosin heavy chain) gene are most common; MYBP-C and troponinT are next in frequency <ul style="list-style-type: none"> ▪ these 3 genes = 70-80% of all cases of HCM

	<ul style="list-style-type: none"> ▪ a.a. substitution 403 Arg→Gln (in β-MHC) = most commonly reported mutation ▪ majority of mutations are single-point missense mutations
Morphology	<ul style="list-style-type: none"> • Massive myocardial hypertrophy w/out ventricular dilation – heart is thick-walled, heavy, and hypercontracting, in contrast to flabby, hypocontracting heart of DCM • Classic pattern = disproportionate thickening of ventricular septum compared to free wall of LV (asymmetrical septal hypertrophy) • Cross-section – ventricular cavity compressed into "banana-like" configuration (bulging of ventricular septum into lumen) • Often present are endocardial thickening or mural plaque formation in the LV outflow tract and thickening of anterior mitral leaflet • Histologic features: extensive myocyte hypertrophy w/ transverse myocyte diameters >40 μm (normal, approximately 15 μm);*** myofiber disarray; interstitial and replacement fibrosis
Clinical Presentation	<ul style="list-style-type: none"> • EF 50-80% (normal) • Reduced chamber size, poor compliance w/ reduced stroke volume results from impaired diastolic filling of the massively hypertrophied left ventricle → exertional dyspnea, harsh systolic ejection murmur, focal myocardial ischemia, angina • Major clinical problems = atrial fibrillation w/ mural thrombus formation and embolization, IE of mitral valve, intractable cardiac failure, ventricular arrhythmias, and sudden death <ul style="list-style-type: none"> ➢ Young athletes
Other	<ul style="list-style-type: none"> • Reduction of the mass of the septum by surgical excision of muscle is done in some cases to relieve outflow tract obstruction

Dilated cardiomyopathy (DCM)	
Etiology	<ul style="list-style-type: none"> • <i>Progressive cardiac dilation and contractile (systolic) dysfunction</i>, us. w/ concomitant hypertrophy (sometimes called congestive Cardiomyopathy)
Epidemiology	<ul style="list-style-type: none"> • 90% of all Cardiomyopathy cases; most commonly affects individuals 20-50 y.o.
Pathophysiology	<ul style="list-style-type: none"> • Causes – Idiopathic; alcohol; peripartum; genetic; myocarditis; hemochromatosis; chronic anemia; doxorubicin (Adriamycin); sarcoidosis; uremia <ul style="list-style-type: none"> ➢ Myocarditis – coxsackie B virus ➢ EtOH abuse – assoc. w/ thiamine deficiency (beriberi heart disease indistinguishable from DCM) ➢ Genetic influence – autosomal dominant is predominant pattern; mutations affect cytoskeleton or mt genes <ul style="list-style-type: none"> ▪ Mt mutations → DCM in children ▪ X-linked form (best understood) → presents in teens, early 20s; rapidly progressive; mutated dystrophin (cell membrane-based cytoskeletal protein, critical for linking internal cytoskeleton w/ external basement membrane) • Indirect myocardial dysfunction = Ischemic heart disease; valvular heart disease; hypertensive heart disease; congenital heart disease

Morphology	<ul style="list-style-type: none"> Heart is us. heavy (weighs 2-3X normal), large and flabby w/ dilation of all chambers; wall thinning accompanies dilation; ventricular thickness may be less than, equal to, or greater than normal Mural thrombi are common; may be source of thromboemboli Histologic abnormalities in idiopathic DCM are nonspecific, us. do not reflect a specific etiologic agent – most muscle cells hypertrophied w/ enlarged nuclei, but many are attenuated, stretched, and irregular
Clinical Presentation	<ul style="list-style-type: none"> EF < 40%; end stage EF < 25% Presents w/ slowly progressive signs and symptoms of CHF (SOB, easy fatigability, poor exertional capacity)
Typical Outcome	<ul style="list-style-type: none"> 50% of patients die w/in 2 years; only 25% survive >5 years Death us. attributable to progressive HF or arrhythmia, can occur suddenly
Other	<ul style="list-style-type: none"> <i>Arrhythmogenic right ventricular cardiomyopathy</i>, or <i>arrhythmogenic right ventricular dysplasia</i> = most commonly assoc. w/ RHF and V-tach; autosomal dominant inheritance w/ variable penetrance <ul style="list-style-type: none"> RV wall severely thinned due to loss of myocytes, w/ extensive fatty infiltration and interstitial fibrosis Naxos syndrome = related disorder w/ similar cardiac findings plus hyperkeratosis of plantar palmar skin surfaces; mutated gene codes for <i>plakoglobin</i> (a.k.a. γ-catenin, intracellular protein that links transmembrane adhesion molecules in desmosomes to desmin, the principal intermediate filament protein in cardiac myocytes)

Restrictive cardiomyopathy	
Etiology	<ul style="list-style-type: none"> Impairment of compliance (diastolic dysfunction) – <i>primary decrease in ventricular compliance, resulting in impaired ventricular filling during diastole</i>; the contractile (systolic) function of the left ventricle is usually unaffected
Pathophysiology	<ul style="list-style-type: none"> Caused by – Idiopathic; amyloidosis; radiation-induced fibrosis Indirect myocardial dysfunction = Pericardial constriction
Morphology	<ul style="list-style-type: none"> Ventricles ~ normal size or slightly enlarged, cavities not dilated, myocardium is firm Biatial dilation is commonly observed Histologic – patchy or diffuse interstitial fibrosis, which can vary from minimal to extensive
Clinical Presentation	<ul style="list-style-type: none"> EF 45-90% Functional state can be confused w/ constrictive pericarditis or HCM
Other	<ul style="list-style-type: none"> <i>Endomyocardial fibrosis</i> = disease of children and young adults in Africa and other tropical areas; unknown etiology; characterized by fibrosis of ventricular endocardium and subendocardium that extends from apex toward tricuspid and mitral valves → fibrous tissue markedly diminishes volume and compliance of affected chambers → restrictive functional defect; large mural thrombi sometimes develop Loeffler endomyocarditis = endomyocardial fibrosis, typically w/ large mural thrombi similar to those seen in tropical disease; assoc. w/ eosinophilic leukemia (abnormal, degranulated eosinophils; major basic protein causes myocardial damage → necrosis) <i>Endocardial fibroelastosis</i> = uncommon heart disease of obscure etiology; characterized by focal or diffuse fibroelastic thickening us.

	involving mural LV endocardium; most common in the first 2 years of life; often accompanied by congenital cardiac anomaly (aortic valve obstruction ~ 30%); rapid and progressive cardiac decompensation and death
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Myocarditis	
Etiology	<ul style="list-style-type: none"> • Inflammatory process is the cause of rather than a response to myocardial injury • Coxsackie A and B and other enteroviruses account for most of cases • Other less common etiologic agents = cytomegalovirus, HIV, <i>Chlamydia psittaci</i>, <i>Rickettsia typhi</i>, <i>Neisseria meningitides</i>, <i>Corynebacterium diphtheriae</i>, <i>Borrelia burgdorferi</i>, <i>Candida</i>, <i>Trypanosoma</i> Chagas disease, <i>Toxoplasmosis gondii</i>, Trichinosis, <i>Strep</i> (rheumatic fever) • Can be related to allergic reactions (<i>hypersensitivity myocarditis</i>), often to particular drugs such as antibiotics, diuretics, and antihypertensive agents • Assoc. w/ systemic diseases of immune origin (RF, SLE, and polymyositis) • Cardiac sarcoidosis and rejection of transplanted heart are also considered forms of myocarditis
Morphology	<ul style="list-style-type: none"> • Ventricular myocardium is typically flabby and often mottled by either pale foci or minute hemorrhagic lesions. Mural thrombi may be present in any chamber • Infective myocarditis = interstitial inflammatory infiltrate (mononuclear, predominantly lymphocytes) and focal necrosis of myocytes adjacent to inflammatory cells • Hypersensitivity myocarditis = interstitial infiltrates, principally perivascular, composed of lymphocytes, macrophages, w/ high proportion of eosinophils • Giant cell myocarditis = widespread inflammatory cellular infiltrate containing multinucleate giant cells interspersed w/ lymphocytes, eosinophils, plasma cells, and macrophages; has at least focal but frequently extensive necrosis; etiology unknown; poor prognosis • Chagas disease myocarditis = distinctive parasitization of scattered myofibers by trypanosomes accompanied by inflammatory infiltrate of neutrophils, lymphocytes, macrophages, and occasional eosinophils
Clinical Presentation	<ul style="list-style-type: none"> • Broad (asymptomatic to sudden death) • Fatigue, dyspnea, palpitations, precordial discomfort, and fever

Pericardial Effusion & Hemopericardium = distention of pericardium by fluid of variable composition (*pericardial effusion*), blood (hemopericardium), or pus (purulent pericarditis)

- Slowly accumulating effusions < 500 mL → only clinical significance is characteristic globular enlargement of heart shadow noted on chest x-ray
- **Rapidly developing fluid collections 200-300 mL (hemopericardium caused by ruptured MI, traumatic perforation, infective endocarditis, or ruptured aortic dissection) → compression of atria, venae cavae, or ventricles → cardiac filling restricted → potentially fatal cardiac tamponade**

Pericarditis = inflammatory reaction in the epicardial and pericardial surfaces with scant numbers of polymorphonuclear leukocytes, lymphocytes, and macrophages; us. secondary to variety of cardiac diseases, thoracic or systemic disorders, metastases from neoplasms arising in remote sites, or surgical procedures on the heart; primary pericarditis rare, us. of viral origin

- **Serous pericarditis** = produced by noninfectious inflammations, such as RF, SLE, scleroderma, tumors, and uremia
- **Fibrinous pericarditis = MOST COMMON type of pericarditis, composed of serous fluid mixed with fibrinous exudate**
 - Common causes = acute MI, **postinfarction (Dressler) syndrome (likely an autoimmune condition appearing several weeks after a MI)**, uremia, chest radiation, RF, SLE, and trauma
 - **Morphology** – surface is dry, with a fine granular roughening
 - Characteristic ***loud pericardial friction rub***
- **Serofibrinous pericarditis** = increased inflammatory process induces more and thicker fluid, yellow and cloudy owing to leukocytes and erythrocytes (may give visibly bloody appearance), fibrin
- **Purulent or Suppurative pericarditis** = invasion of pericardial space by infective organisms; predisposed by immunosuppressive therapy
 - **Morphology** – thin to a creamy pus of up to 400 to 500 mL in volume; serosal surfaces are reddened, granular, and coated with the exudate; acute inflammatory reaction microscopically
 - Sometimes the inflammatory process extends into surrounding structures
→ **mediastinopericarditis**
 - Often produces constrictive pericarditis
- **Hemorrhagic pericarditis** = most commonly due to malignant neoplasm involving pericardial space; can also be due to **TB, bacteria, underlying bleeding diathesis; often occurs following cardiac surgery**
- **Caseous pericarditis** = occurs w/ TB (sometimes w/ fungi); RARE, but still the MOST FREQUENT antecedent of disabling, fibrocalcific, chronic constrictive pericarditis
- **Chronic pericarditis = organization** produces plaque-like fibrous thickenings of serosal membranes ("solider's plaque") or thin, delicate adhesions of obscure origin; observed often at autopsy; rarely cause impairment of cardiac function
- **Adhesive mediastinopericarditis** = may follow suppurative or caseous pericarditis, previous cardiac surgery, or irradiation to mediastinum; pericardial sac is obliterated; **increased workload causes cardiac hypertrophy and dilation, mimicking DCM**
- **Constrictive pericarditis** = pericardial space is obliterated; heart is surrounded by dense, adherent layer of scar with or without calcification, often 0.5 to 1.0 cm thick; can resemble a plaster mold in extreme cases (*concretio cordis*); surgical removal of the cast (pericardectomy)

Primary Cardiac Tumors

- **Myxoma** – MOST COMMON primary cardiac tumor in adults; most often in left atrium; derived from differentiation of primitive multipotential mesenchymal cells; *** **favored site is fossa ovalis in atrial septum (left atrium)**
 - **opening snap and accentuated first heart sound**
 - **“ball-valve” effect causes functional malignancy**
 - Carney syndrome (autosomal dominant transmission) = multiple cardiac and extracardiac myxomas, spotty pigmentation, endocrine overactivity
- **Lipoma** – subendocardium or subepicardium; poorly encapsulated; may produce arrhythmias

- **Papillary fibroelastoma** – may represent organized thrombi; Lambl excrescences on aortic valves
 - Histologically – covered by endothelium, deep to which is myxoid connective tissue containing abundant mucopolysaccharide matrix and elastic fibers
- **Rhabdomyoma** – MOST COMMON primary cardiac tumor in kids; hamartomas; may be due to defect in apoptosis during developmental remodeling; high assoc. w/ tuberous sclerosis; small gray-white masses w/ spider cells
- *Sarcoma* – angiosarcomas and other sarcomas not morphologically different than those at other locations