Pathology Review Flash Cards for Revision
Vascular, Cardiology, Pulmonary, Hematology

Spring 2009

**PAN (polyarteritis nodosa)**
- Medium sized muscular arteries
  - Spares lungs
- Young adults
  - 30% HBV Ag+, not associated with ANCA
- Type III fibrinoid necrosis
  - two stages found at the same time
    - Acute- transmural neutrophil, eosinophils, and mononuclear cells
    - Chronic- fibrous vessel thickening, mononuclear cells
  - Leads to aneurysmal nodules in skin and organ infarction (renal failure, acute MI, bloody diarrhea, ulcers)
  - Kidney disease major cause of death but NO glomerulonephritis involved

**Leukoclastic vasculitis (micro-PAN)**
- Necrotizing vasculitis of small vessels: arterioles, capillaries, venules
- **Micropolyangitis=leukocytoclastic vasculitis**
  - all lesions same stage (ACUTE), unlike PAN
  - fragmented PMNs in vessel walls w/ fibrinoid necrosis
  - p-ANCA (+) but no immune complexes found ("pauci-immune")
  - necrotizing glomerulonephritis, hemoptysis, palpable purpura
  - Immune rxn. to drug, infection, tumor. Resolves on removal of causative agent

**Takayasu’s Arteritis**
- Fibrosis, irregular thickening and narrowing of aortic arch & great vessels
- Involvement of root of aorta may - dilatation with aortic valve insufficiency; involvement of coronary ostia may lead to MI
- Affects Asian women < 40 y.o.
- Granulomatous inflammation w/ mononuclear infiltrate & giant cells
- “Pulseless disease” with weak upper extremity pulses
- Ocular disturbances, hypertension
- Fever, arthritis, myalgia, night sweats

**Temporal (Giant Cell) Arteritis**
- Involves arteries of the head: temporal >> ophthalmic, vertebral, aorta
  - ?immune response to elastin
  - Granulomatous inflammation w/ giant cells, lymphocytes, eosinophils, and neutrophils
  - Nodular wall thickenings w/ reduction in lumen size
  - Affects elderly patients > 50
  - Headache, visual disturbance, blindness, jaw claudication, palpable temporal artery
  - Fever, fatigue, weight loss
  - Associated w/ polymyalgia rheumatica
  - Treat with corticosteroids to prevent blindness

**Wegener’s**
- Vasculitis of small arteries & veins of middle-aged men
  - c-ANCA +
  - Mostly involves Lungs and Upper Airways
    - acute necrotizing granulomas—→ focal necrotizing vasculitis
    - central area of necrosis surrounded by lymphs, plasma cells, macros, giant cells
  - Also involves Kidneys
    - acute focal proliferative or diffuse crescentic necrotizing glomerulonephritis
    - ulcerative lesions of nose, palate, pharynx; associated with nosebleeds and hemoptysis; chronic sinusitis, pneumonitis
  - Hematuria, proteinuria, renal failure
  - Very poor prognosis
### Kawasaki’s/ Buerger’s

<table>
<thead>
<tr>
<th><strong>Kawasaki’s Syndrome</strong> affects children &lt;4yo</th>
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<tbody>
<tr>
<td>Disease of young children (most &lt;4 years); Epidemic in Japan, Hawaii</td>
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<tr>
<td>Acute segmental necrosis with pronounced inflammation and necrosis resembling PAN</td>
</tr>
<tr>
<td>Vasculitis of large &amp; medium arteries, esp. coronary arteries</td>
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<td>Mostly self-limited but may cause acute MI/sudden death</td>
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<td>Fever, skin rash (erythema of palms and soles, rash with desquamation), cervical adenopathy, oral/conjunctival erythema (“strawberry tongue”) (mucocutaneous lymph node syndrome)</td>
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<td>TX: IV IgG &amp; Aspirin</td>
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<thead>
<tr>
<th><strong>Buerger’s Disease</strong> affects heavy smokers &lt;age 35</th>
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<tbody>
<tr>
<td>Idiopathic segmental thromosing vasculitis of small &amp; medium peripheral arteries = “thromboangiitis obliterans”</td>
</tr>
<tr>
<td>Involves tibial and radial arteries</td>
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<tr>
<td>Intermittent claudication, superficial nodular phlebitis, cold sensitivity, autoamputation of digits</td>
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<tr>
<td>Raynaud’s disease - Not associated with organic lesions</td>
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<tr>
<td>Raynaud’s phenomenon - Vascular insufficiency secondary to thromboangiitis obliterans, SLE, and systemic sclerosis</td>
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### Churg-Strauss

<table>
<thead>
<tr>
<th><strong>Churg-Strauss</strong></th>
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<tbody>
<tr>
<td>Small vessels : skin, lung, heart</td>
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<tr>
<td>Eosinophil-rich granulomatous reaction</td>
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<td>Affects atopic people</td>
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<tr>
<td>Associated with allergic rhinitis, asthma and blood eosinophilia</td>
</tr>
<tr>
<td>P-ANCA in 70%</td>
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<tr>
<td>Coronary arteritis and myocarditis</td>
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<tr>
<td>Most common cause of morbidity and mortality</td>
</tr>
<tr>
<td>Pulmonary necrotizing vasculitis</td>
</tr>
<tr>
<td>Henoch Schonlein Purpura: affects children</td>
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<tr>
<td>Segmental fibrinoid necrosis with IgA deposition</td>
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<tr>
<td>Sequela to upper respiratory infection (maybe post-strep)</td>
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<tr>
<td>Palpable purpura, arthralgia, abdominal pain w/ intestinal hemorrhage, renal damage, fever</td>
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### Atherosclerosis

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<th><strong>Pathogenesis</strong></th>
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<tr>
<td>Local cell injury → accumulation and oxidation of lipid (LDLs) → endothelial cell activation &amp; increased vascular permeability → adhesion/influx of platelets &amp; monocytes into intima → secretion of cytokines → further influx of inflammatory cells → migration/activation of smooth muscle cells &amp; fibroblasts → secretion of collagen &amp; ECM components</td>
</tr>
<tr>
<td>Oxidized lipid appears to play a central role – they are chemotactic for monocytes, † inflammatory cytokines, † macrophage motility and are toxic to endothelial cells/smooth muscle</td>
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<tr>
<th><strong>Atherosclerosis</strong></th>
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<tbody>
<tr>
<td><strong>Fatty streaks</strong> (earliest lesions) contain foam cells with variable amounts of proteoglycans, extracellular lipid and T cells – <em>can be seen in toddlers</em></td>
</tr>
<tr>
<td>Lesions progress with age → become raised → coalesce into plaques</td>
</tr>
<tr>
<td>Over time, fibrotic plaque becomes unstable → “fracture” → exposure of collagen promotes platelet adhesion and local thrombus formation</td>
</tr>
<tr>
<td>Fissuring or rupture of a plaque can produce emboli and acute infarctions at distant sites (e.g MI)</td>
</tr>
<tr>
<td>Lipid/cholesterol emboli a particular problem in the kidney</td>
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Atherosclerosis

- **Distribution**: abdominal aorta > coronary arteries > popliteal arteries > descending thoracic aorta > internal carotids > circle of willis → occurs at branching points, ostia of vessels
- **Major Risk Factors**: hypertension, smoking, hyperlipidemia/ hypercholesterolemia**, diabetes
- **Key components**:
  - fibrous cap
  - core of cellular debris, foam cells, cholesterol crystals
  - "shoulders" with activated cells, foam cells, migrating/proliferating smooth muscle cells
- **NOTE**: hypothyroidism assoc with hypercholesterolemia**

Varicosities

- Varicose veins are abnormally distended, lengthened and tortuous veins
- Most commonly located at the superficial saphenous vein, they can also be found in the distal esophagus (portal HTN), anorectal region (hemorrhoids), or scrotum (varicocele)
- Caused by incompetence of the venous valves which can be exacerbated by pregnancy, prolonged standing, obesity, oral contraceptives, and age
- There is a familial association
- They can develop secondary to DVTs which cause dilation of the veins

Deep Venous Thrombosis

- Typically caused by Virchow's Triad:
  - 1. Stasis (causes the release of procoagulants such as thromboplastin from endothelium leading to localized coagulation)
  - 2. Hypercoagulable state (Factor V leiden, cancer)
  - 3. Trauma
- lower extremity below the knee; also often seen in the superficial saphenous, hepatic and renal veins
- In the lower extremities they typically extend toward the heart.
- can weaken and break off typically leading to embolization to a pulmonary artery.
- Prevent with anticoagulant therapy (heparin, warfarin)

Atherosclerosis Clinical Features

- ↓ Blood flow = end organ ischemia → in diabetics, associated with gangrene of the extremities
- Intermittent ischemia of lower extremities, **claudication**= cramping of muscles not getting enough oxygen (especially w/ exertion)
- ↓ Blood flow in renal circulation → salt and water retention via renin-angiotension system
- Compromised coronary circulation = exertion ischemia and angina (not MI)
- Ischemia of media → weakening of wall → aneurysm

Aneurysms and Dissections

- Berry/saccular Aneurysm
  - Congenital weakness in wall
  - Usually around Circle of Willis (Acomm is #1)
  - Rupture in young adults
  - Subarachnoid hemorrhage
  - Associated with Ehlers Danlos, polycystic kidneys, Marfan's

Aneurysms and Dissections

- Aortic Aneurysm (fusiform, cylindrical)
  - Caused by severe atherosclerosis with hypertension
  - Most common between renal and iliac arteries
  - Complications: rupture, embolism (from atheroma, mural thrombus), occlusion of vertebral vessels
  - Other aortic aneurysms
    - Myotic - infection (Salmonella): media destruction
    - Luetic - syphilis: aortic arch aneurysm (from damage to media) with tree-barking (intima damage), dilation of aortic valve → insufficiency/cor bovinum
Aneurysms and Dissections

• Aortic Dissection
  – Follows tear in tunica intima
  – Occurs within tunica media
  – Result of hypertension, connective tissue disease
  – Most common cause of death: hemopericardium
  – Also causes aortic valve insufficiency; compromise of coronary, renal, mesenteric, and/or iliac arteries
  – Sudden onset anterior chest pain that moves

• Cystic medial necrosis
  – No necrosis present (bad terminology)
  – Associated with fusiform aneurysms, aortic dissections
  – Changes: tissue fragmentation, small cystic spaces with amorphous material, no inflammation
  – See in patients with Marfan’s, Ehlers-Danlos

Syphilitic Heart/Aortic Disease

• Seen in tertiary syphilis
• Most commonly involves proximal aortic root
• Mechanism: small vessel vasculitis
  – Infiltration of lymphocytes and plasma cells in vasa vasorum, destruction of vascular supply leads to loss of media layer
  – Loss of elasticity causes aortic dilation
  – Characteristic “tree barking” appearance of wrinkled intima due to scar formation and contraction in underlying musculature
• Consequences: aneurysm and/or dissection
  – Dilation of aortic root leads to aortic valve insufficiency
    • Subsequent development of cor bovinum
  – Can have rupture of aneurysms
  – Occlusion of coronary ostia possible
• Luetic aneurysms
  – assoc. w/ tertiary syphilis
• Confined to thoracic aorta: usually aortic arch
  – “Cor Bovinum”- enlarged heart secondary to AI
• Inflammation of adventitia
  – Obliterative endarteritis of vasa vasorum
  – Lymphocytic and plasmacytic infiltrate
• Treebarking of aortic intima from segmental wrinkling from scar contraction
• Assoc. w/ aneurysmal dilation AND dissection

Hypertension - Types

• Essential (Primary) Hypertension – idiopathic, 95% of cases and does not cause short term problems
• Secondary Hypertension – Renal or adrenal disease, narrowing of renal artery, renal insufficiency.
• Malignant Hypertension – 5% of patients can show a rapidly rising blood pressure that can lead to death within a year or two. Pressures can exceed 200/120 and often develops in a patient with pre-existing hypertension.

Hypertension - Causes

• Blood Pressure = Cardiac Output X Peripheral Resistance
• Increased Cardiac Output – Increased volume due to sodium retention or water retaining hormones. Increased contractility due to neural or hormonal stimulation
• Increased Peripheral Resistance – Increased production of constrictors (Angiotensin II, Catecholamines, Thromboxane) Reduced production of dilators (prostaglandins, kinins, NO). Neural factors Alpha-adrenergic (constrictor) beta-adrenergic (dilator)
Hypertension - Morphology

- Renal
  - Hyaline Arteriosclerosis – Homogeneous, pink, hyaline thickening of arterioles with a narrowing of the lumen. This is most often associated with essential hypertension and diabetes. This is a major morphologic characteristic of benign nephrosclerosis.
  - Hyperplastic (Malignant) Arteriosclerosis – Related to acute or severe elevations of blood pressure. Characterized by “onion skinning” which is a thickened and reduplicated basement membrane.
- Heart – concentric left ventricular hypertrophy
  - Thickened fibers, internalized duplicated nuclei

Vascular Tumors

- Hemangioma
  - Capillary- “birth mark”
    - Thin-walled, lined by endothelial cells
    - Bright red to blue, slightly raised
    - “strawberry type” - newborns, grows rapidly but fades at 103 years, regresses by age 5
  - Cavernous
    - Red-blue, soft spongy mass
    - From formation of large cavernous vascular channels
    - May rupture (if large) or cause thrombosis
    - Not usually clinical significant (cosmetic mainly)
      - Most common benign tumor of liver and spleen

- Glomus tumor
  - Benign tumor from smooth muscle cells of the glomus body (arteriovenous anastomoses involved in thermoregulation)
  - Anywhere in the skin or soft tissue, very painful
    - Most commonly found in the distal portion of the digits under the nail bed
    - Small elevated, red-blue firm nodules
  - Histology
    - Branching vascular channels separated by stromal elements
    - Cells are small, round or cuboidal with scant cytoplasm with nests typically arranged around vessels from arteriovenous shunts in glomus bodies

Angiosarcomas, Kaposi’s sarcoma (KS)

- Malignant endothelial neoplasms, seen in blood and or lymphatic vessels
- All degrees of differentiation of tumors can be seen
- Liver angiosarcoma associated w/ polyvinyl chloride
- Kaposi’s sarcoma
  - Associated with HHV-8 and immunosuppression (i.e. HIV)
  - Vascular tumor arising from mesenchymal tissue
  - Lesions contain inflammatory cell infiltrates and spindle cells → proliferation and angiogenesis
  - See patches that are pink-purple macules, can turn into raised plaques and even nodules in later stages. May be painful
  - Classic/European KS uncommon in US and not associated w/ HIV; Endemic or African KS is lymphadenopathic and aggressive
  - Most common cancer in AIDS;

Ischemic Heart Disease

- Imbalance between supply ( perfusion) and demand of the heart for oxygenated blood. Also reduced availability of nutrients and inadequate removal of metabolites
  - Spectrum:
    - MI(Acute Ischemia) – Ischemia is sufficient to cause death of cardiac muscle
    - Anigna Pectoris (Intermittent Ischemia) – Ischemia is less severe, no death of cardiac muscle
    - Heart Failure (Chronic Ischemia) - Chronic ischemic myocardial damage and progressive onset of CHF

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Ischemic Heart Disease

- Stable Angina: Pain precipitated by exertion and relieved by rest or by vasodilators. Results from severe narrowing of atherosclerotic coronary vessels that are unable to supply sufficient oxygenated blood to increased myocardial demands of exertion.
- Unstable Angina: Prolonged or recurrent pain at rest, often indicative of imminent MI
  - Disruption of atherosclerotic plaque with superimposed thrombosis
- Prinzmetal Variant Angina: intermittent chest pain at rest, considered to be due to coronary artery vasospasm
**Ischemic Heart Disease**

- Atherosclerosis of coronary arteries leads to narrowing of the lumen (coronary artery disease)
- This can lead to:
  - Hypertension causes myocardial hypertrophy and a subsequent increase in oxygen demand
  - Increased oxygen demand → Angina → Chronic Ischemia → Heart Failure
  - Formation of a thrombus on an atherosclerotic plaque → acute ischemia and myocardial infarction
  - Transmural Infarction- Entire thickness of myocardium (acute)
  - Subendocardial Infarction – inner portion, at greatest risk for poor perfusion – can occur with chronic subcritical stenoses

**Myocardial Infarction**

- **LCA:**
  - LCX (left circumflex): LA, posterior wall of LV
  - LAD: LV anterior, apex, anterior portion of v. septum

- **RCA:** RA, RV, 25-35% of LV
  - SA Nodal: SA node
  - Acute marginal: RV
  - PDA: inf. wall, v. septum, posteromedial papillary mm. (supplied by LCX 15% of people)

- Infarct: LAD>RCA>LCX

**Myocardial Infarction – Time Course**

- over first few hours, cells begin to change from acute cell injury to necrosis - coagulative necrosis with loss of nuclei and hyper-eosinophilic fibers
- edema and separation of fibers is first visual sign of inflammation
- neutrophils must migrate into necrotic area; takes 2-4 days for cellular infiltrate to be prominent
- subacute phase follows with macrophages and lymphocytes
- fibrosis occurs over next several weeks
- tissue becomes weakest and most vulnerable to rupture after 4-5 days
- eventual replacement of myocardium with fibrous scar (weeks)

**Myocardial Infarction – Complications**

- dysfunctional heart muscle
- Arrhythmias
  - within minutes; most common cause of death
- extensions of the infarct
- aneurysm/dilatation
- ventricular rupture (septal or free wall)
  - Only after 4-5 days
- mural thrombus
- pericardial effusion/pericarditis
- papillary muscle infarction

**Myocardial Infarction**

- **Enzymes**
  - Troponin I/T: rises after 4h, peaks 24-48h, normal at 7-10d
  - CK-MB: rises in 4-8h, peaks 24h, normal at 48-72h

- **EKG**
  - Q-wave MI: ST elevations, transmural infarct
  - Non-Q-wave MI: nonspecific ST/T wave changes or ST depression, subendocardial infarct

- **Morphology**
  - 4-24h: coag. necrosis, contraction band necrosis (due to ROS formation and Ca²⁺ influx on reperfusion)
  - 2-4d: hyperemia, loss of nuclei and striations, neutrophils then macrophage infiltrate
  - 5-10d: yellow-brown softening, granulation tissue (risk of rupture)
  - 7wks: scar complete

**Congenital Heart Disease**

- Separation of right heart from left heart
  - VSD – most common congenital heart disease
  - ASD
- Separation of atria from ventricles
  - Tricuspid
  - Mitral
- Division of pulmonary and arterial outflow
  - Pulmonic
  - Aortic
  - Truncus arteriosus
  - Transpositions of the Great Arteries
**Congenital Heart Disease**
- Development of junction between valves & ventricular wall
  - Tetralogy of Fallot
    - Degree of pulmonary stenosis determines degree of cyanosis
  - Endocardial cushions – Down Syndrome
- Closing of ductus arteriosus
  - PDA
    - Remains open with PG synthesis – treat with aspirin
    - Closes when PG no longer synthesized – treat with PGE
    - Cyanosis involves toes, not fingers
- Development of aortic arch
  - Coarctation of the aorta
    - Infantile pre-DA
    - Adult form post DA

**Cyanosis**
- Cyanosis can be early or late (tardive)
- If flow directly from right to left, early cyanosis
  - 4 T's: Tricuspid atresia, Tetralogy of Fallot, Truncus arteriosus, Transposition
- Right ventricle and pulmonary artery do not respond well to increased volumes or pressures
  - With time, pulmonary artery pressures increase and flow reverses
  - No cyanosis early on; cyanosis after reversal – takes years and results only after irreversible pulmonary hypertension has developed
- Sometimes an opening must exist for a baby to survive
  - Blood can only get to the lungs two ways: thru the pulmonic valve or thru a PDA
  - Oxygenated blood can get to the left side of the heart four ways: thru the left atrium, thru an ASD, thru a VSD or thru a PDA; but the routes are limited by flow considerations

**Other**
- Malpositions of the heart
  - Dextrocardia with situs inversus
    - Kartagener’s syndrome - triad of: situs inversus (transposition) of the viscera, abnormal frontal sinuses producing sinusitis and bronchiectasis, and immobility of the cilia
  - Eisenmenger’s syndrome
    - an underlying heart defect that allows blood to pass between the left and right sides of the heart
    - pulmonary hypertension, or elevated blood pressure in the lungs
    - polycythemia, an increase in the number of RBC's
    - the reversal of the shunt
- Components of Tetrology of Fallot – what determines flow (degree of pulmonary stenosis)
- Machinery mumur in PDA

**Bicuspid Aortic Valve**
- Congenital bicuspid valve ➔ calcification of cusps ➔ calcific aortic stenosis
- *Heaped-up, calcified masses within aortic cusps* - nodules restricted to base and lower ½ of cusps
- Architectural distortion of valve with impaired function
- Microscopic → *fibrosed and thickened cusps*
- Little functional significance at birth- predisposes to calcification in adult life – 6th to 7th decade

**Infective Endocarditis**
- Infection of mural endocardium (heart valves)
  - usually bacterial (95%), also fungal, chlamydia, rickettsia,
  - Staph epidermidis infects prosthetic valves
  - Mitral > Aortic valve; Tricuspid valve in IV drug users
- Produces bulky friable vegetations composed of thrombotic debris, fibrin, inflammatory cells & organisms
  - Symptoms: fever, new onset heart murmur (right sided lesions may be asymptomatic), fatigue
  - If left-sided ➔ systemic emboli can cause janeway lesions (in palms or soles), brain abscess, nail bed hemorrhages
  - Requires long-term antibiotic therapy

**Infective Endocarditis**
- Acute Endocarditis
  - Staph aureus infection of the endocardium, often secondary to infection somewhere else in the body (bacteremia)
  - Heart valves often previously normal
  - L side > R side
  - Rapidly progressive destructive lesions, high fever, can be fatal
  - Necrotizing, ulcerative, invasive lesions
  - Complications: Ring abscesses – erosion into underlying myocardium, Septic systemic emboli
Infective Endocarditis

- **Subacute Endocarditis**
  - Strep Viridans, oral commensals
  - Occurs in setting of pre-existing valvular disease like rheumatic heart disease, collagen exposure, abnormal flow pattern, shunts
  - L side > R side
  - Slowly progressive lesions, low fever, most recover
  - Antibiotic prophylaxis for dental procedures if pre-existing valvular lesions – bacteremia of oral commensals
- **IV drug use Endocarditis**
  - Staph aureus (also candida, aspergillus, gram negatives like pseudomomas)
  - R side > L side (MC: tricuspid valve) b/c of venous drainage

Non-bacterial Endocarditis

- **Non-bacterial Thrombotic Endocarditis**
  - Small masses of fibrin, platelets on cardiac valves
  - Lesions are sterile and non-destructive
  - Pancreatic cancer, other malignancy, Swan-Ganz catheter
- **Libman-Sacks disease (SLE)**
  - Sterile, granular pink vegetations that are destructive, causing fibrinoid necrosis
  - May be present on undersurfaces of valves
  - Verrucae with fibrinous material, hematoxylin bodies
- **Carcinoid Heart Disease**
  - Right heart valves; fibrous intimal thickenings with smooth muscle cells in mucopolysaccharide-rich matrix

Rheumatic Heart Disease

- Sterile, but associated with group A strep
- Fibrinoid necrosis with inflammatory cells
  - Aschoff body- pathognomonic for rheumatic fever
  - Focal interstitial inflammation consisting of fragmented collagen and fibrinoid material, large Anitschokow myocytes and multinucleated giant cell (Aschoff cell)
  - Anitschokow (Aschoff) cells- plump activated histiocytes, surround Aschoff bodies
- Lead to cusp fusion along cusp line
- Mitral +/- aortic valve
  - Leading cause of mitral stenosis (chronic disease)
  - Mitral regurgitation in acute disease

Myocardial Disease

- **Hypertrophic - IHSS**
  - the walls of the ventricles and septum are greatly thickened
  - diastolic dysfunction and insufficient forward flow
  - myofiber disarray; the myocytes are hypertrophied, in a haphazard array, surrounded by interstitial and replacement fibrosis
  - Hypertrophy of the interventricular septum, results in outflow obstruction
  - sudden death in young athletes, atrial arrhythmias, mural thrombi
  - 50% familial; autosomal dom. with variable penetrance

Myocardial Disease

- Dilated
  - all four chambers are enlarged -- global dilation (large, rounded heart)
  - The primary dysfunction is systolic: flabby, hypocontracting heart
  - 20-60 yrs old; slowly developing CHF
- **Restrictive**
  - it is characteristically firm and noncompliant
  - chamber is non compliant and cannot fill normally (diastolic dysfunction); systolic function of the ventricle is unaffected
  - Bi-atrial dilatation is commonly observed
  - Amyloidosis, lymphomas

Pericarditis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Morphology</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>Inflammatory reaction in epicardial and pericardial surfaces</td>
<td>Vitreous pericarditis; Non-infectious inflammation; Rheumatic fever, lupus, scleroderma, tumors, uremia</td>
</tr>
<tr>
<td>Fibrinous or Suppurative</td>
<td>Serous fluid mixed with fibrinous exudate; Organization of exudate may result, but may resolve</td>
<td>MOST FREQUENT TYPES OF PERICARDITIS: Acute myocardial infarction, Dressler's syndrome (post myocardial immune-mediated disease), UREMIA, chest radiation, lupus, Rheumatic fever, trauma</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>Suppurative exudate; Sensory nerves reddened, granulat, and covered with exudate; Organization is usual outcome and may result in constriction pericardia</td>
<td>Infection of pericardial space by infective organisms; Direct extension, bacteria; lymphatic extension, direct introduction during cardiotomy; Immuno suppression potentiates all pathways; Spiking temperatures, chills, and fever</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>Blood mixed with fibrinous or suppurative effusion</td>
<td>Tuberculosis, direct neoplastic involvement of the pericardial space, fibro, tumors, or bleeding disorder</td>
</tr>
<tr>
<td>Caseous</td>
<td>Caseation</td>
<td>Tubulization from two within tracheobronchial nodes</td>
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Infectious Myocarditis

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<td>Viral myocarditis:</td>
<td>Interstitial mononuclear (lymphocytic) infiltration</td>
<td>Most common cause of myocarditis; assoc. with infants, immunosuppressed, pregnant women</td>
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<tr>
<td>Coxsackie A, B</td>
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<tr>
<td>HIV</td>
<td>Focal necrosis of myocytes</td>
<td>Usually follows primary viral infection elsewhere</td>
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<tr>
<td>ECHO, Polio, Influenza</td>
<td>Post-infectious fibrosis</td>
<td>May have an immune component; first humoral anti-viral response followed by T-cell mediated damage</td>
</tr>
<tr>
<td>Parasitic diseases:</td>
<td>Parasitism of myocytes with scattered inflammatory infiltrate</td>
<td>Protozoal South American myocarditis; may affect 50% of cases; causes progressive cardiac insufficiency due to chronic immune-mediated damage; die 20 yrs. later</td>
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<tr>
<td>Chagas’ Disease</td>
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<tr>
<td>Trypanosoma cruzi</td>
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<tr>
<td>Trichinella</td>
<td>Encysted Trichinella with inflammatory infiltrate, eosinophils</td>
<td>Most common helminthic disease; may affect 50% of cases; causes progressive cardiac insufficiency due to chronic immune-mediated damage; die 20 yrs. later</td>
</tr>
<tr>
<td>Bacterial diseases:</td>
<td>Patchy myocyte necrosis with sparse lymphocytic infiltrate</td>
<td>Mediated by diptheria exotoxin</td>
</tr>
<tr>
<td>Corynebacterium diphtheriae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Spirochete infection of myocytes</td>
<td>Occurs in 2/3 of cases; causes progressive cardiac insufficiency due to chronic immune-mediated damage; die 20 yrs. later</td>
</tr>
</tbody>
</table>

Toxic Myocardial Diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Morphology</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Dilated myocardial disease</td>
<td>Direct toxic effect by alcohol and its metabolites (acetaldehyde)</td>
</tr>
<tr>
<td>Nutritional (Beriberi)</td>
<td>Dilated myocardial disease</td>
<td>Thiamine deficiency, of ten assoc. with chronic alcoholism</td>
</tr>
<tr>
<td>Adriamycin (Doxorubicin, daunorubicin)</td>
<td>Myofiber swelling and vacuolization, fatty change, myocytolysis</td>
<td>Anthracyclin chemotherapeutic agents Dose-dependent Lipid peroxidation of myofiber membranes</td>
</tr>
<tr>
<td>Catecholamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripartum state</td>
<td>Globally dilated heart</td>
<td>Associated with hypertension, volume overload, nutritional deficiency; Reversible</td>
</tr>
</tbody>
</table>

Pulmonary Edema

- Left heart failure
- Findings
  - Alveolar edema (transuduate)
  - Few alveolar red cells
  - Congestions
  - Heart failure cells
  - Pleural effusion – straw-colored fluid

Pulmonary Hypertension

- Pressures >25 cm Hg
- Chronic better tolerated than acute
- Smooth muscle hyperplasia with narrowing of lumen
- Cor pulmonale with right heart failure
- Hyperplastic arteriolosclerosis and even atherosclerosis
- Clinical associations
  - Cyanotic heart disease
  - Long-standing restrictive or obstructive lung disease
- Primary pulmonary hypertension- young to middle aged women
  - Mutation of BMPR2 (bone morphogenic receptor)
    - In absence of BMPR2 signalling, proliferation of vascular smooth muscle occurs
    - Plexiform arteriopathy
    - Formation of capillary tuft or web that spans the lumen
- Secondary – restrictive lung disease, congenital heart disease

Pulmonary Emboli

- Thromboembolism
  - associated with deep vein thrombosis in hypercoaglable states, immobility, phlebothrombosis
  - Can also be fat (post fracture), amniotic fluid (obstetrical disaster), or gas embolism
- Causes ventilation-perfusion mismatch
  - Leads to decrease in oxygenation
- Clinical
  - most small emboli are silent
  - Saddle embolus - sudden death with electromechanical dissociation
  - Can lead to wedge-shaped hemorrhagic infarct

Obstructive Pulmonary Diseases

- Expiratory airflow obstruction
- FEV1 decreased more than FVC
  - FEV1/FVC ratio less than 70% (normal ratio = 80%)
- Hyperinflation with increased FVC
- Pulmonary hypertension can occur with long-standing obstructive disease
  - Most commonly with emphysema
  - right heart failure – cor pulmonale
Obstructive Pulmonary - Asthma

- **Extrinsic Asthma (Allergic)**
  - Usually begins in childhood, often with family history of atopy
  - Type I hypersensitivity to environmental allergen – IgE mediated
- **Intrinsic Asthma (Non-atopic/non-immune)**
  - Associated with aspirin, pulmonary viral infections, cold, exercise, stress
- **Acute phase (minutes to hours)**
  - Mast cell degranulation
- **Late phase (hours to days)**
  - Mediated by leukocytes
  - Eosinophils, basophils, neutrophils
  - Edema & infiltrates exacerbate luminal narrowing
  - Damage to tissue by enzymes/cytokines (eosinophil major basic protein)

Obstructive Pulmonary - Asthma

- Presents with attacks of dyspnea, wheezing, cough
- **Morphology:**
  - Hyperinflation of lungs
  - Smooth muscle hypertrophy
  - Thickened basement membranes
  - Goblet cell hyperplasia
  - Mucus plugs with whorl accumulations of shed epithelial cells (Curschmann’s spirals)
  - Prominent eosinophilia (5-50% of cells)
  - Crystalloid eosinophil membrane protein (Charcot-Leyden crystals)
  - Inflammatory cell infiltrate (late phase reaction)

Obstructive Pulmonary - Emphysema

- **Pathogenesis:**
  - ↑ protease (elastase) activity via ↑ stimulation or ↓ inhibition
  - Protease/elastase released from neutrophils and macrophages.
  - Destruction of elastic lung tissue; loss of elastic recoil
  - Permanent enlargement of respiratory part of bronchial tree with fusion of alveoli to form blebs/bullae (rupture = pneumothorax)
  - Collapse/Obstruction of terminal airways upon expiration

Obstructive Pulmonary - Emphysema

- Types (proximal vs. distal vs. entire acinus respectively):
  - Centriacinar: most severe in upper lobes; associated with smoking
  - Paraseptal: most severe in upper lobes near pleura, septa
  - Panacinar: most severe at base; associated with ↓ α-1-antitrypsin

Obstructive Pulmonary - Emphysema

- **Clinical:**
  - Asymptomatic until late in the disease
  - Prolonging/slowing of forced expiration
  - ↓FEV1, ↓FVC, ↓FEV1/FVC (< 0.7), ↑TLC
  - Barrel chest (↑ A-P diameter)
  - Normal O2, ↑CO2
  - Weight loss (↑ caloric expenditure for respiration)
  - ***Peripheral (O2) chemoreceptors drive respirations due to chronic high CO2. O2 administration may inhibit respiratory drive and lead to respiratory arrest!***
  - “Pink Puffer”

Obstructive Pulmonary – Chronic Bronchitis

- Diagnosis: persistant cough + sputum for at least 3 months in at least 2 consecutive years, associated with smoking & pollution
- Submucosal gland hypertrophy → increase in Reid index
  - Reid index = gland depth/total thickness of bronchial wall
  - >50% in chronic bronchitis
- **Morphology:**
  - Hypertrophy of submucosal glands in trachea & bronchi
  - Goblet cell hyperplasia in small bronchi & bronchioles – leads to mucus plugging of small airway lumens
  - Inflammatory infiltrate w/ fibrosis of bronchial wall
- **Clinical:** sputum, dyspnea on exertion, mild cyanosis, recurrent pulmonary bacterial infections, can lead to cor pulmonale
  - Severe airflow obstruction can lead to coexisting emphysema
Obstructive Pulmonary - Emphysema

- Permanent dilatation of air spaces beyond terminal bronchiole
  - Destruction of alveolar walls w/o fibrosis
  - Due to imbalance between proteases (mainly elastase) & anti-proteases (mainly \( \alpha \)-antitrypsin) in the lungs
- Loss of elastic recoil \( \rightarrow \) collapse of airways on exhalation
- **Centroacinar** - Involves respiratory bronchioles of upper lobes
  - Associated w/ smoking, coal worker’s pneumoconiosis
  - Smoking attracts neutrophils & macrophages (both of which secrete elastases), and decreases \( \alpha \)-antitrypsin activity
  - Increased elastase activity results in loss of structure & recoil
- **Panacinar** - Involves the entire acinus of the lower lobes
  - Associated w/ \( \alpha \)-antitrypsin deficiency (homozygous piZZ phenotype)

Restrictive Lung Disease

- Chronic alveolitis (usually in peripheral zones) causes inflammatory infiltrate with cytokine production which leads to fibrosis, which decreases oxygen diffusion and can lead to pulmonary HTN and cor pulmonale
- Capacity measurements \( \downarrow \) (decreased CO diffusion capacity/lung volume/compliance)
- \( FEV1/FVC = \uparrow \) (>80%)
- Interstitial fibrosis, chest wall abnormality, or neuromuscular DI are underlying factors
- Secondary impairment of capillary flow, pulmonary HTN, & cor Pulmonale
  - Final common pathway of restrictive lung disease
  - Pulmonary HTN, cor pulmonale irreversible

Pneumoconiosis

- Pneumoconiosis = non-neoplastic lung reaction to inhalation of mineral dusts
  - 1-5 um \( \rightarrow \) most dangerous size b/c reaches terminal airways & engulfed by MØ
- Caused by exposure to asbestos, silica, or carbon
- Caplan’s Syndrome = RA + pneumoconiosis

Coal Worker’s Pneumoconiosis

- Three forms
  - 1) Anthracosis - asymptomatic; urban dwellers
  - 2) Simple CWP - collagen nodules & coal macules adjacent to bronchioles; affects upper lobes most; centrilobular emphysema may occur
  - 3) Complicated CWP - progression of simple CWP
    - necrotic & fibrotic nodules; intensely blackened scars

Asbestosis

- Most common lesion = benign fibrous pleural plaque (caused by cytokine damage to diaphragm, asbestos fibers NOT present in plaques)
- **DIFFUSE INTERSTITIAL** (vs. Silicosis [nodular])
- Most common Cancer = bronchogenic Ca (smoking synergism)
- \( 2^{nd} \) most common CA = mesothelioma (v. malignant)
- Ship yard pipe fitter/ roofer; spear-like asbestos bodies
- 2 forms:
  - 1. serpentine chrysotiles (curly/flexible, cause fibrosis but NOT mesothelioma bc cilia can remove)
  - 2. Amphibole (straight/stiff; impale epithelium, reside in interstitium; form golden brown colored dumbbells)

Silicosis

- Sandblaster or foundry worker (rock & quartz)
- Slow progression of nodular, fibrotic masses;
  - Filled with hard silica crystals; eggshell LN calcification
- Upper lung zones
- Increased risk of TB!
- Slightly increased risk of bronchogenic carcinoma
Sarcoidosis

- noncaseating granulomas
- most common in lungs, but also seen in H&N (salivary gland enlargement), skin nodules
  - laminated calcium & protein concretions
  - stellate inclusions w/in giant cells – asteroid bodies
- bilateral hilar adenopathy
- insidious onset of dyspnea, SoB, hemoptysis
- Dx by exclusion
- ↓ in CD4 T Helper cells b/c used up in granuloma
- anergy and hypercalcemia

Other Restrictive

- Hypersensitivity Pneumonitis
  - Farmer’s Lung- inhaled actinomyces or aspergillus
  - Silo Filler’s DI- inhaled NO2 gas from fermentation
- Goodpasture’s Disease
  - starts w/ hemorrhagic pneumonitis; anti-GBM
- Idiopathic Pulmonary Fibrosis
  - type III hypersensitivity
  - alveolitis→fibrosis→honeycomb lung (fibrotic lung w/cystic spaces)

Other restrictive lung dz – radiation (radiation pneumonitis)

- Common cause is radiation treatment for CA in the thorax, neck, or abdomen
- Acute changes (occur 1-6 mos after therapy)
  - Similar to those in adult respiratory distress syndrome
  - Loss of type II cells → loss of surfactant
  - Leaky capillaries → deposition of hyaline membranes
  - fever, dyspnea, and radiologic infiltrates
  - Diffuse alveolar damage with SEVERE ATYPIA of hyperplastic type II pneumocytes
  - patients respond to steroid therapy
- Chronic changes
  - Septal fibrosis
  - Bronchiolar metaplasia
  - Hyaline thickening of blood vessels

Other restrictive lung dz – Drugs

- direct injury to lung tissue by cytotoxic drugs
  - Amiodarone used to treat resistant cardia arrhythmias; preferentially concentrated in the lung and causes pneumonitis in 5-15%
- secondary to hypersensitivity vasculitis (ex. drug-induced lupus)
  - Can be seen in trt with: procainamide, hydralazine, isoniazid, clindamycin
- secondary to bronchospasm (ex. due to aspiration, allergies, β-antagonists, or cholinergic agonists)

Other restrictive lung diseases- RA, Lupus, Scleroderma

- RA→ interstitial fibrosis, pulmonary nodules (nodules can cavitate, causing pneumothorax or bronchosophageal fistulas)
- Lupus→ interstitial inflammation can lead to fibrosis
- Scleroderma→ lung involvement (in general) is leading cause of death, chest wall fibrosis can cause restrictive ventilatory defects

Other Interstitial Lung Diseases

- Berylliosis (All age groups, M=F)
  - Ag-specific CD4 response to beryllium; direct irritation potentiates
  - Hilar lymphadenopathy and non-caseating granulomas that organize into fibrous nodules; birefringent calcite bodies (Schaumann’s bodies)
  - Histologically indistinguishable from sarcoidosis
  - Can cause obstructive, restrictive, or diffusion defect
  - Beryllium lymphocyte proliferation test is diagnostic
  - Responds to steroids and smoking cessation
Other Interstitial Lung Diseases

- Desquamative Interstitial Pneumonitis (4th or 5th decade, M>F)
  - Virtually always smoking-related
  - Massive aggregation of mononuclear cells in alveoli with lipid and PAS-positive granules and surfactant-containing lamellar bodies
  - Restrictive and diffusion defect; dyspnea, dry cough, clubbing of digits
  - Responds to steroids and smoking cessation

- Wegener’s granulomatosis (peak in 5th decade, M>F)
  - Systemic necrotizing granulomatous vasculitis of small/medium vessels
  - Necrotizing granulomas of respiratory tract with associated capillaritis
  - Focal necrotizing glomerulonephritis, often with crescents; nephritic
  - Cavitary infiltrates on CXR, chronic sinusitis, ulceration of nasopharynx
  - Cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) present

- Pulmonary alveolar proteinosis (20-50 years old, M>F)
  - 90% of cases unknown etiology; possibly impaired surfactant clearance due to anti-GM-CSF antibodies
  - Homogenous, granular PAS-positive precipitate in alveoli consisting of all three surfactant proteins; marked increase in lung size/weight
  - Slowly progressive dyspnea, productive cough with chunks of gelatinous material

- Bronchiolitis Obliterans
  - chronic inflammation + prolonged effort to resolve/organize pulmonary injury
  - Continuous bronchiolar injury and repair leads to pulmonary compromise involving loose fibrous plugs in the bronchioles
  - Distal airways plugged with organizing exudate in response to infection or inflammatory injury
    - Exudate: polypoid plugs of loose, fibrous tissue
    - common response to infection/inflammation
  - Causes: infection, inhaled toxins, drugs, collagen vascular disease, bronchial obstruction
  - cough and dyspnea

Pulmonary Infection: Pneumonia

- Sx: chills, fever, productive cough, SOB, pleurisy
- Lobar: pneumococcus, intra-alveolar exudate
  - congestion, red then gray hepatization, resolution
- Broncho: Strep pyogenes, H. Flu, klebsiella, Staph. aureus
- infiltrate from bronchiole to alveoli, patchy

- Mycoplasma pneumoniae: most common, “walking pneumonia”
  - young adults/kids
  - Symptoms of upper respiratory infection, minimal sputum
  - Interstitial mononuclear infiltrates
  - Cold agglutinins
  - Legionella, Chlamydia pneumoniae (trachomatis in newborns)
  - Respiratory syncytial virus: young children, upper respiratory infection, mononuclear infiltrates, may occur in epidemics
  - Influenza virus - neuraminadase and hemagglutinin mutations
  - Coronavirus - SARS
  - Adenovirus
### Pneumonia - Causes

- **Typical Community-acquired**
  - Presents: lower lobe patchy consolidation, sudden fever with productive cough
  - **Diagnose:** CXR is gold standard,
    - G+ stain, increased tactile fremitus,
    - **Strep. pneumoniae** is MC

- **Atypical Community-acquired**
  - Presents: interstitial pneumonia, insidious onset, nonproductive cough, low grade fever. No consolidation.
  - **Diagnose:** mononuclear infiltrate, CXR,
    - **Mycoplasma pneumoniae** is MC
    - Others: Chlamydia pneumoniae (TWAR agent), Viruses (RSV, Influenza, adeno), Chlamydia trachomatis (newborns).

- **Nosocomial**
  - Presents: patients with severe underlying disease, antibiotic therapy, immunosupression, respirators
  - **Diagnose:** culture
    - **Pseudomonas** is MC (from respirators)
    - Others: **E. coli**, gram positives like **Staph aureus**.

- **Immuino-compromised**
  - Presents: Complication of AIDS and bone marrow transplant
    - **Pneumocystis** is MC (TMP-SMX for prophylaxis and treatment).
  - Others: CMV, **Aspirgillus**

### Pulmonary Infection: Tuberculosis

- **1°:** initial infection
  - usually asymptomatic
  - Ghon complex- subpleural granuloma and associated hilar lymph nodes
    - Upper part of lower lobe or lower part of upper lobe
    - Caseous necrosis, Langhan giant cells, X-ray may show calcification

- **2°:** reactivated
  - Cavitory lesion - Involves one or both apices
  - Hemoptysis, fever, pleural effusion (bloody), weight loss, drenching night sweats

- **3°**: miliary
  - lymphatic or hematogenous spread
    - other organs: psoas abscess, Pott’s disease (vertebrae)

### Pulmonary Infection: Lung Abscess

- **Causes**
  - complication of bacterial pneumonia
  - bronchial obstruction (cancer)
  - aspiration (LOC from alcohol/drugs, neurological disease
  - **Staph**, pseudomonas, klebsiella, proteus, other anaerobic organisms
  - **Symptoms**
    - fever, foul purulent sputum
    - fluid-filled cavity on X-ray
  - **Bronchiectasis:** chronic necrotizing infection of bronchi
    - leads to abnormal dilation of airways (increased dead space)

### Pulmonary Infection: Bronchiectasis

- permanent bronchial dilatation; caused by chronic necrotizing infection (ie TB, staph, mixed infection)
- **PATH:** airway wall damage -> loss of elasticity/dilation -> disruption of pressures/air flow -> sputum trapping/obstruction -> infection -> further damage to walls -> more dilatation/“swiss cheese”-like dilatations of bronchioles to pleura
- presents with cough, fever, massive purulent smelly sputum production, hemoptysis, and recurrent infection
- predisposed by bronchial obstruction, chronic sinusitis/bronchitis, asthma, cystic fibrosis
- part of Kartagener’s syndrome (chronic sinusitis, bronchiectasis, and situs inversus)

### Cystic Fibrosis

- **Mucoviscidosis**, fibrocystic disease of the pancreas
- Autosomal recessive dis. found primarily in whites
  - **Cause:** mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7

- **Characteristics:**
  - Malfunction of exocrine glands resulting in:
    - Increased viscosity of mucus- secretions dehydrated in bronchioles, pancreatic ducts, bile ducts, meconium and seminal fluid
    - Increased chloride concentration in sweat (basis of sweat test)

- **Sweat test:** important diagnostic procedure
  - Secretion of chloride and sodium normal, reabsorption impaired
**Cystic Fibrosis**

- **Clinical Manifestations**
  - *Chronic pulmonary disease*
    - Retention of viscous mucus leading to secondary infections; recurrent pneumonia, severe chronic bronchitis, bronchiectasis, and lung abscess
  - *Pseudomonas aeruginosa* infection is a common cause of death
  - *Pancreatic insufficiency*
    - Deficiency of pancreatic enzymes leading to malabsorption and steatorrhea
  - *Meconium ileus*
    - Small bowel obstruction in newborn due to thick, viscous meconium

**Malignant Pulmonary Neoplasms**

- Most common is metastatic
- Small Cell Carcinoma - Central Mass w/ paraneoplastic syndrome
- Squamous Cell Carcinoma - a central hilar mass/cavitation
- Large Cell-clear cell and spindle cell types
- Adenocarcinomas:
  - Bronchioalveolar-central neoplasm mimicking pneumonia
  - Bronchial-derived-develops on a site of prior inflammation
  - Others: carcinoid-neuroendocrine derived tumor located in major bronchi may produce Carcinoid syndrome like GI

**Bronchogenic Carcinoma – General features**

- The leading cause of death from cancer in both sexes
- Arise from 1st, 2nd, or 3rd order bronchi and thus are found centrally as a hilar mass; those that arise in the periphery are adenocarcinomas
- Irregular warty projections that either fungate into the lumen or infiltrate along the wall
- The lesion is normally gray-white and firm
- Can extend into the pleura causing a friction rub
- Most common site of Metastases include the adrenals, liver, brain, and bone

**Bronchogenic Carcinoma**

- Leading cause of death from cancer in both men and women, peaks in 6th and 7th decades
- Directly proportional in incidence to number of cigarettes smoked daily and to the number of years of smoking
- Histological changes:
  - squamous metaplasia of respiratory epithelium
  - with atypical changes ranging from dysplasia to carcinoma in situ, which precedes bronchogenic carcinoma in smokers
- Genetic Factors:
  - Occasional familial clustering
  - c-myc in small cell; K-ras in adenocarcinomas
  - p53

**Other causes:**
- Air pollution
- Radiation- increased incidence in radium and uranium workers
- Asbestos- increased incidence with asbestos exposure and greater incidence with asbestos plus cigarette smoking
- Industrial exposure to nickel and chromates; also exposure to coal, mustard gas, arsenic, beryllium and iron
- Previous Injury
  - Scarring- usually adenocarcinoma
  - Causative or desmoplastic response to tumor

**Squamous Cell Carcinoma**

- characterized by the production of keratin and intracellular bridges
- Bronchogenic
  - appears as a central hilar mass
    - If localized, surgery may be curative
  - often cavitory (due to necrosis)
- Paraneoplastic Syndrome
  - ectopic PTH-like activity causing hypercalcemia
- Highly related to smoking
- Most common cause of Pancoast's tumor
### Small (Oat) Cell Carcinoma
- Highly malignant centrally located
- The most aggressive bronchogenic carcinoma
- These tumors are often widely metastatic at diagnosis and, not resectable, respond well to chemotherapy
- Morphology: Tumor cells have scant cytoplasm and resemble lymphocytes, but twice the size (OAT CELL)
- Associated with SIADH or ACTH paraneoplastic syndromes
- Incidence is greatly increased by smoking

### Bronchial Carcinoid
- ~1-5% of lung tumors
- Neuroendocrine cell origin -> may secrete neuropeptides such as serotonin
  - Carcinoid syndrome – diarrhea, flushing, cyanosis (systemic symptoms)
  - May be locally invasive; metastasis possible, but rare
  - Growth into lumen -> symptoms of obstruction; local invasion
  - Not related to smoking!
  - Most often follows benign course with 50-95% 5-10 year survival

### Other Lung Tumors
- **Large cell carcinoma**
  - ~10% of lung cancers
  - Marked anaplasia, larger polygonal cells
  - thought to be undifferentiated squamous cell or adenocarcinoma
  - Cells contain mucin, may see multinucleate giant cells
- **Bronchial Carcinoid**
- 1-5% of lung tumors
- Neuroendocrine cell origin -> may secrete neuropeptides such as serotonin
  - Carcinoid syndrome – diarrhea, flushing, cyanosis (systemic symptoms)
  - May be locally invasive; metastasis possible, but rare
  - Growth into lumen -> symptoms of obstruction; local invasion
  - Not related to smoking!
  - Most often follows benign course with 50-95% 5-10 year survival

### Bell's Palsy
- Lower motor neuron palsy causing facial paralysis
- Inflammation of CN VII (facial nerve)
  - Inflammation near stylomastoid foramen or in bony facial canal
- Association with HIV, sarcoidosis and Lyme disease
  - In Lyme disease often a bilateral palsy
- Clinical findings include: difficulty speaking, inability to close eye, and drooping of corner of mouth

### Non-bacterial Endocarditis
- **Non-bacterial Thrombotic Endocarditis**
  - Small masses of fibrin, platelets on cardiac valves
  - Lesions are sterile and non-destructive
  - Pancreatic cancer, other malignancy, Swan-Ganz catheter
- **Libman-Sacks disease (SLE)**
  - Sterile, granular pink vegetations that are destructive, causing fibroinoid necrosis
  - May be present on undersurfaces of valves
  - Verrucae with fibroin material, hematoxylin bodies
- **Carcinoid Heart Disease**
  - Right heart valves; fibrous intimal thickenings with smooth muscle cells in mucopolysaccharide-rich matrix

### External/Internal Ear
- **External Ear**
  - Cauliflower ear – secondary to trauma (wrestling)
  - Otitis Externa – Pseudomonas in diabetics
  - Carcinomas – generally rare; basal/squamous cell carcinoma of the pinna is more common
- **Internal Ear**
  - Otitis Media – generally S. pneumoniae, S. aureus, or Moraxella; in the diabetic patient, Pseudomonas infection is common → necrotizing otitis media
  - Cholesteatoma – associated with otitis media; cystic lesions lined by keratinizing squamous epithelium w/ or w/o cholesterol spicules; can erode ossicles/labyrinth
  - Otosclerosis – fibrous ankylosis of footplate leading to stapes anchoring, leads to hearing loss over time
Middle Ear

- **Otitis Media**
  - Most common causes = Strep pneumoniae, H flu, Staph aureus, Moraxella
  - Often secondary to viral infection
  - Mastoiditis = rare complication
  - Chronic can lead to aural polyps and ossicle resorption
  - Serous form is non-suppurative
    - Eustachian obstruction by tonsil hyperplasia/recurrent infection, allergies, assoc w/hearing problems
- **Tumors (rare):**
  - Cholesteatoma: epidermal cyst; resembles keratin pearl; cholesterol crystals; Squamous Cell Carcinoma

Internal Ear

- **Deafness** - mechanical vs. neural
  - Neural - degeneration, compression of nerves, inflammation
  - Mechanical - bone pathology, fluid, etc.
- **Inflammation**
  - Otitis - bone deposition along stapes foot plate; conductive hearing loss in young adults
  - Meniere's Disease - vertigo, nystagmus, nausea, tinnitus, hearing loss; hydroptic dilatation of endolympathic system of cochlea
  - Labyrinthitis - infectious (viruses; mumps, CMV, rubella) and post-infectious (follows upper respiratory virus)
- **Tumors**
  - Acoustic neuroma - neoplasm of Schwann cells of 8th cranial nerve in the internal auditory canal

Nose/Sinuses

- **Rhinitis**
  - Infectious (usually viral [adeno-, echo-, rhino-])
  - Atopic (IgE-mediated, recurrent → POLYPS = hypertrophic swellings, edematous stroma)
- **Sinusitis:**
  - Acute inflammation → obstruction → infection by S. pneumoniae, H. flu, M. cat; S. aureus
  - Mucor; assoc w/diabetes; may extend into bone/other sinuses
  - Kartagener's: bronchiectasis, situs inversus, sinus infect. Bc defective cilia
  - Wegener's granulomatosis: acute necrotizing granulomas; involve lung; c-ANCA

- **Neoplasms:**
  - BENIGN
    - Juvenile angiofibroma (non-metastasizing, hemorrhagic)
    - Inverted papilloma
  - MALIGNANT:
    - Nasopharyngeal carcinoma (EBV-assoc, children in Africa/China, poor prognosis)
    - Lethal midline granuloma (T-cell lymphoma; necrotizing/ulcer)
    - Plasma cell carcinoma (normal lymph structure)
    - Olfactory neuroblastoma (radiation-sensitive)

Pharyngeal Cancers, Laryngeal Pathology

- **Nasopharyngeal Carcinomas**
  - Seen in children in Africa, adults in southern China, and in all ages in US (rare), males> females
    - Associated with EBV
  - Types: keratinizing squamous cell, nonkeratinizing squamous cell, undifferentiated (known for prominent lymphocytic infiltrate and syncytial cells)
  - Silent onset, metastasis present at diagnosis
- **Larynx**
  - Inflammation (Laryngitis)- Common in children (croup) and smokers chronic → important predisposition to development of squamous cell carcinoma

Pharyngeal Cancers, Laryngeal Pathology (cont)

- Reactive Nodules- smooth, round, sessile, small on true vocal cords
  - Heavy smokers and singers
  - Do NOT give rise to cancer
- **Laryngeal Carcinoma (squamous cell)**
  - Smoking most common cause, alcohol (synergistic with smoking), squamous papillomas (HPV 6 and 11)
  - Preceded by hyperplasia-likelihood of carcinoma proportional to degree of atypia
  - Pearly plaques → fungating, ulcerated lesions; on true vocal cords
  - Hoarseness, hemoptysis, cervical lymphadenopathy
**Remnant Malformations**

- **Thyroglossal Duct Cyst**
  - Cysts dilate from mucinous, clear secretions → 2-3 cm. masses
  - Anterior to trachea, in the midline

- **Branchial Cleft Cyst**
  - On anterolateral neck, 2-5 cm. in diameter
  - From branchial arch remnants or salivary gland inclusions in cervical lymph nodes
  - Cysts with fibrous walls and intense lymphocytic infiltrate

- **Craniopharyngioma**
  - Rathke pouch remnant
  - Lamellar keratin, cysts with cholesterol-rich fluid, calcifications

**Oral Cancer and Candidiasis**

- **Majority** are well-differentiated *squamous cell carcinomas*, mainly seen in males with a history of tobacco use, alcohol use, chronic denture irritation, and an association with HPV infection.
  - p16 gene inactivation, loss of p53, overexpression of cyclin D

- **Location**: 1. Lower lip (along vermillion border) 2. Floor of mouth 3. Lateral border of tongue.
  - Early lesions appear as erythroplakia

**Salivary Gland Tumors**

- **Basal cell carcinomas** also seen – most common site is upper lip, heavily associated with UVB exposure.

- **Candidiasis** – seen in neonates, immunocompromised (pre-AIDS lesion), diabetes mellitus patients, and following treatment with broad spectrum antibiotics.

**Anemias of Decreased Production**

- *all have Reticulocyte count that is low* (less than 1-3%) even in the presence of low Hb and low Hct

- **Symptoms of Anemia of any type**: Dyspnea on exertion, weakness, fatigue, dizziness, insomnia, anorexia, Headache, angina → anemia can reveal hidden coronary artery disease.

- **Low MCV** (less than 75): Iron deficiency, Anemia of Chronic Disease, Sideroblastic Anemia (Alcohol, lead, B12 deficiency), Thalassemias

- **Normal MCV** (80-95): Aplastic Anemia, Chronic Renal Disease (low Erythropoietin), Metabolic Disease (hypothyroid), Marrow damage (tumor, drugs), Cancer of marrow: acute leukemias, myelofibrosis

- **High MCV** (greater than 100): B-12 deficiency (pernicious anemia); Folate deficiency, Nitrous oxide, Hydroxyurea
### Microcytic, Hypochromic Anemia (Low MCV)
- **Iron Deficiency Anemia**: Bone marrow reticuloendothelial cells = dec. stainable iron
  - Decreased Serum Iron
  - Decreased Ferritin
  - Increased Total iron binding capacity (TIBC) aka transferrin
  - Dec % Saturation of Transferrin (%sat = serum iron/TIBC x 100)
- **Anemia of Chronic Disease**: rheumatoid arthritis, endocarditis, neoplasms
  - Decreased Serum Iron
  - Increased Ferritin
  - Increased % Saturation
  - Decreased TIBC
  - (iron is sequestered away from blood to keep it away from blood pathogens, but there is plenty of iron in the body)

### Iron Deficiency Anemia
- #1 Nutritional disorder in the world → In world, due to iron deficiency in diet;
- in US, due to chronic blood loss → iron deficiency anemia indicates a GI bleed (loss of iron in stool) → think COLON CANCER until proven otherwise (do an occult blood stool test!) in a man or postmenopausal female
  - think menorrhagia/menstrual loss in female of reproductive age
    - decreased hemoglobin synthesis
    - hypochromic, microcytic
    - symptoms: koilonychia, pallor, pale conjunctiva
    - increased RDW (RBCs = variable in size)

### Normocytic Anemia = Aplastic Anemia
- Normocytic, normochromic anemia (MCV = 80-99)
- Causes: Radiation, Chemotherapy, Infections: Parvovirus B19, Hepatitis C, Chronic renal disease (decr. Erythropoietin as well as uremia toxicity), Fanconi’s anemia, Drug reactions
- Morphology: hypcellular bone marrow with increased fat predominating
- Patient needs transfusions → hemosiderosis/iron overload
- Clinical findings: no splenomegaly, low reticulocyte index
- Can see pancytopenia: anemia (pallor, fatigue), thrombocytopenia (petechiae), increased infections

### Megaloblastic Anemias (increased MCV)
- **B12/Folate Deficiency** 
  MCV>100
  - Bone Marrow = hypercellular with megaloblasts because nuclei cannot condense and mature due to a defect in DNA synthesis → ineffective erythropoiesis.
  - Hypersegmented neutrophils in peripheral blood smear.
  - All rapidly dividing cells are affected by DNA synthesis problem. Exhibit large immature nuclei (ex. Mucosal cells of the GI trad), not just RBC precursors
  - Megaloblasts in bone marrow can crowd out other stem cells and lead to leukopenia and thrombocytopenia in addition to anemia
  - B12 and folate are both needed to synthesize nucleic Acids
  - B12 is a cofactor for Homocysteine Methyltransferase which helps regenerate Tetrahydrofolate (THF). THF is then used to synthesize thymine.
  - Vitamin B12 deficiency is manifest as homocysteinemia.

### Folate Deficiency → No neurological signs!
- The major cause of folate deficiency is decreased intake in diet, especially in Alcoholics – only a few months worth of folate is stored in the body (unlike B12 which has enough stored for years)
  - major dietary source = green leafy veggies
- Phenytoin inhibits the absorption of folate in the jejunum by blocking intestinal conjugate and can also decrease folate deficiency
- Methotrexate inhibits Dihydrofolate Reductase leading to folate def. (can’t reduce dihydrofolate to tetrahydrofolate)
- Can see pancytopenia: anemia (pallor, fatigue), thrombocytopenia (petechiae), increased infections

### B12 Deficiency
- B12 Deficiency → defective DNA synthesis → asynchronism between cell division and hemoglobin synthesis → Megaloblastic anemia
- Urine methymalonic acid increased and serum homocysteine levels are elevated, serum B12 may be decreased
- Macrocytosis, leukopenia with hypersegmented granulocytes, mild to moderate thrombocytopenia
- Increased hemolysis may lead to iron overload
### B12 Deficiency—Neurologic Complications

- **B12 Deficiency but not Folate Deficiency** may include neurological complications—B12 more likely due to malabsorption and folate due to dietary insufficiency.
- Increased levels of methylmalonate may lead to abnormal fatty acids that may be incorporated into neuronal lipids and produce neurological complications.

#### Subacute Combined Degeneration
- Degeneration of lateral and posterior columns of spinal cord (decreased vibration, light touch, joint proprioception) AND upper motor neuron signs due to lateral column demyelination; Bilateral symptoms; Dementia 2° to CNS demyelination.
- Microscopic: diffuse spongy degeneration of the white matter, myelin and axonal degeneration, macrophage response and gliosis.

### B12 Deficiency Causes

- **Decreased intake:**
  - Strictly vegetarian diet, Malabsorption, achlorhydria, gastrectomy, diffuse intestinal disease or resection (Crohn’s), decreased intrinsic factor (pernicious anemia), exocrine pancreas dysfunction
  - Increased requirement: Pregnancy, hyperthyroid, Cancer, Fish tapeworm (Diphyllobothrium latum)

### Anemias (increased destruction) - Intro

- Anemias of increased destruction are known as hemolytic anemias.
- Two pathways are associated w/ hemolytic anemia
  1. Extravascular (i.e. phagocytosis)
  2. Intravascular (i.e. lysis)

- **Extravascular** is predominate form. It is associated w/ RBC damage and/or coating with Ab or complement followed by destruction in RES.
  - Hb released outside vessels (no hemoglobinemia, no hemoglobinuria, no drop in haptoglobin)
  - ↑ Hb metabolism → unconjugated hyperbilirubinemia
  - Splenic erythropagocytosis → splenomegaly

### Anemias (increased destruction) — Immunohemolytic/extravascular

- Immunohemolytic anemia (anti-RBC Ab) results in positive direct Coombs test.
  - *Warm Ab* (IgG, common, idiopathic/CLL/SLE/drugs)
    - Membrane loss → spherocytosis → trapped in spleen
  - *Cold Agglutinin* (IgM, C3b, acute, possible M. pneumonia, mono, monoclonal gammopathy)
  - *Cold Hemolysis* (IgG binds at low temp, cmplmt then binds and causes intravascular hemolysis at warm temp (paroxysmal cold hemoglobinuria). Follows mycoplasma, mumps, and flu infections

### Anemias (increased destruction) — Intravascular/trauma

- Intravascular mechanism include mechanical (artfcl heart valves, vascular obstruction), complement, and toxic (C. diff, malaria)
- Microangiopathic anemia is secondary to narrowing or obstruction of microvasculature (DIC, TTP, HUS, SLE, malignant HTN)
- Damage to RBCs results in burr cells (sliced RBCs), helmet cells (loss of membrane), triangle cells, schistocytes (RBC fragments)
- Decreased haptoglobin

### Anemias (increased destruction) — key lab findings

- **Intravascular hemolysis**
  - Hemoglobinemia, hemoglobinuria, extremely low haptoglobin, methemoglobinemia/uria, urine hemosiderosis, increased unconjugated bilirubin, increased urine urobilinogen

- **Extravascular hemolysis**
  - Slightly decreased haptoglobin, increased unconjugated bilirubin, urine urobilinogen, little or no free Hb in blood
Sideroblastic Anemia

• Etiology
  – Inherited (rare): ALA synthase is the rate limiting step in heme synthesis that is dependent on pyridoxine (B6) as a cofactor
  • X-linked: ALA-synthase enzyme (located on X chromosome)
  • Other: Dominant and recessive forms thought to be associated with defects in genes that regulate ALA synthase formation
  – Associated with myelodysplastic syndrome
  – Drugs & Toxins:
    • Large amounts of alcohol interfere with pyridoxine metabolism
    • Lead inactivates enzymes necessary for heme synthesis
    • Isoniazid results in B6 deficiency

β-Thalassemias

• Mutation in β-chain of HbA leading to premature death of RBCs, in marrow and peripherally. Increased iron absorption, transfusions, and increased phagocytosis of RBCs leads to iron overload and hemosiderosis.
• Disease is not only due to decreased hemoglobin production, but is also caused by aggregation of the remaining hemoglobin and removal by the spleen. (splenomegaly and hepatomegaly; hemosiderosis of liver, spleen, pancreas, and myocardium)
• Severe anemia results in expansion of red marrow in thinning of cortical bone (evident in facial bones and maxilla—spares mandible) and extramedullary hematopoiesis.
• Most frequent in Mediterranean countries, Africa & Southeast Asia

β-Thalassemia—Major vs. Minor

• β-chain gene located on chromosome 11
 • Thalassemia Major = homozygous loss of normal β gene (β0/β0, β+/β+, β0/β+)
   – Severe anemia, apparent after 6-9 months (HbF → HbA)
   – Small colorless RBCs; target cells; reticulocyte count increased; normoblasts in periphery
   – HbF is increased and may be major Hb, also HbA2
   – Death in third decade
 • Thalassemia Minor = heterozygous loss of normal β gene (β0β, β+/β)
   – More common, usually asymptomatic, may protect from Malaria
   – Hypochromia, microcytosis, basophilic stippling, target cells; HbA2
   – Must differentiate from iron deficiency anemia
   β0=absence, β+=abnormal, HbF=α2γ2, HbA=α2β2

Alpha Thalassemias

• The most common form of Thalassemias in Southeast Asia caused by DELETIONS of one or more of the four Alpha-globulin genes located on chromosome 16 resulting in defective heme synthesis
• Symptoms Depend on the number of gene deletions:
  • -a/aa: Asymptomatic/Silent
  • --/aa: More Common in Africa-microcytic anemia
  • -a/-a: More Common in Asia-microcytic anemia
  • --/-a: Hemoglobin H disease-severe anemia
    – Heinz bodies and target cells on smear
  • --/--: Hb Barts-hydrops fetaelis/death in utero
    – Anisocytosis and poikilocytosis w/immature RBC on smear

Hemoglobin H Disease (α-Thalassemia)

• Results from a deletion of three of the three alphaglobulin chain genes on chromosome 16.
• Results in the pathologic formation of Betamicroglobulin tetramers called HbH (β4).
• HbH has an increased affinity for oxygen and thus is not useful for oxygen exchange due to its inability to release oxygen to the peripheral tissues.
• In addition, cells are unable to withstand oxidative stresses creating a shortened half-life.
• Produces a mild to moderate anemia
Red Cell Indices

- Low Reticulocyte count
  - MCV (<80) \( \rightarrow \) microcytic anemia
    - Chronic iron deficient anemia, Thalassemias, anemia of chronic disease, sideroblastic anemia
    - MCH (27-32) \( \rightarrow \) iron deficiency anemia – hypochromia
  - Normocytic anemia (MCV 80-100) Acute iron deficiency, aplastic
  - Macrocytic anemia (MCV>100) – Vitamin B12, folate deficiency
- High Retic count: Acute blood loss, hemolysis, membrane defects
- Calculations
  - MCV = (hematocrit/RBC) x 10
  - MCH = (Hb/RBC) x 10
  - MCHC = (Hb/hct) x 100

Hematology Clinical Pathology

- Increased red cell distribution width (RDW) \( \rightarrow \) Measures anisocytosis (Low RDW suggests congenital or chronic defect)
- Reticulocyte count (0.5-1.5%), may increase to 12-15% with blood loss, hemolysis.
- Low reticulocyte count (<2%) with anemia may indicate inability to make new cells.
- Absent reticulocyte count indicates aplastic anemia.

Hematology Clinical Pathology

- Differential \( \rightarrow \) neutrophils (50-70%), lymphocytes (25-35%), monocytes (4-6%), eosinophils (1-3%), basophils (<1%)
- Lymphocytes – 50% T-cells, 25% B-cells, 25% NK cells
  - CD 4 : CD 8 \( \rightarrow \) 2 : 1
- Changes in WBC with age – on day of birth, WBC is between 9,000 to 30,000. Until age 8, lymphocytes more predominant than neutrophils
- Bands – normally between 3-5%
  - increased with inflammation (left shift)(bacterial infection)
- Platelets normally 150,000-400,000
  - < 100,000 = petechiae and bruising ; < 25,000 = spontaneous bleeding

Clinical Pathology – Hematology

Lab values and anemia

<table>
<thead>
<tr>
<th>Serum Fe</th>
<th>chronic disease</th>
<th>hemochrom</th>
<th>pregnancy</th>
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<tr>
<td>↓</td>
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Thalassemias will have normal Iron Studies

Hemoglobin Processing in Intravascular Hemolysis

RBC lysis \( \rightarrow \) Hb binds to haptoglobin and taken up by RES cells \( \rightarrow \) depletion of haptoglobin \( \rightarrow \) free Hb oxidized to MetHb \( \rightarrow \) kidney excretion \( \rightarrow \) Prox. Tubule cells take up hemosiderin and slough off

Leads to hemosiderinuria, methemoglobinemia, hemoglobinuria, increased retic count

Clinical Pathology – Hematology

RBC Hemolysis

- Peripheral smear
  - schistocytes
  - erythrocytes
- Haptoglobin
  - decrease/absent
  - mild decrease
- Urine hemosiderin
  - ++ negative
- Urine Hb
  - ++ negative
- Direct Coombs
  - usually negative
  - +++
- LDH
  - increase
- Jaundice
  - mild

Additional Studies – osmotic fragility test (spherocytosis), HbA2 and HbF levels (thalassemias), Serum B12 and serum folate, serum lead, HbS (sickle cell)

Clinical Pathology – Hematology

- Myeloproliferative Disorders – Polycythemia Vera
  - Proliferation of pluripotent stem cell leads to increased RBC mass, granulocytes, and platelets
  - Primary disorder is increase in Hct to >60% with normal PaO₂, increased plasma volume, hyperuricemia (WBCs dying and purines metabolized)
  - Increased hematocrit inhibits EPO secretion.
  - Differentiates it from 2⁰ polycythemia (COPO, high altitudes)
  - Thick blood leads to thrombotic or hemorrhagic comp., headache, dizziness, GI symptoms, generalized pruritis after temperature change (basophil degranulation)
  - Bone marrow eventually becomes fibrotic over time, leading to extramedullary hematopoiesis blast crisis/AML
### Myeloproliferative Disorders – Myeloid Metaplasia with Myelofibrosis

- Initial proliferation of megakaryocytes and release of TGF-β leads to fibrosis of bone marrow and extra-medullary hematopoiesis, esp. spleen
- Immature RBC (nucleated) and WBC in peripheral blood
- Teardrop RBC’s, anemia, megakaryocytosis, thrombocytosis and thrombosis.
- MASSIVE splenomegaly
- Death from infection, thrombosis.

### G6PD deficiency

**Epidemiology**
- X linked recessive, protective against malaria
- Mediterranean, blacks

**Path**
- NADPH and GSH in pentose phosphate path
- Low GSH yields build up of H202 in RBCs
- Peroxide oxidizes Hb which precipitates (Heinz)

**Presents**
- Hemolytic anemia after oxidative stress (infections, primaquine, dapsone, sulfas, fava beans)

**Labs**
- Normocytic anemia, Heinz bodies

### Spherocytosis

**Path**
- Autosomal dominant
- RBC membrane protein defect results in decreased membrane and spherocytes
  - Ankyrin mutation leads to decrease in spectrin

**Presents**
- Extravascular hemolysis: splenomegaly, jaundice
- Increased permeability of spherocytes to Na (diagnostic) (osmotic fragility test)

### Paroxysmal nocturnal hemoglobinuria (PNH)

**Path**
- Mutation causing loss in Decay accelerating factor (DAF)
- No DAF means complement destroys RBCs

**Presents**
- Intravascular hemolysis
- Episodic hemoglobinuria
- Increased thrombosis risk

**Labs**
- Normocytic anemia, pancytopenia
- Urine Hb
- Sucrose hemolysis test is positive

### Coagulopathy: platelet function

- Platelet count ok; increased bleed time, mucosal bleeding
- **Platelet adhesion**: platelets can’t bind endothelium
  - Bernard-Soulier: AR, unusually large platelets lack of GPIb platelet surface glycoprotein
- **Platelet aggregation**: platelets can’t bind other platelets
  - ASA acetylation/inactivation of COX-1 causing decreased TXA2
  - Glanzmann thrombasthenia: hereditary, deficiency of GPIIb-IIIa on platelet surface; platelets can’t form fibrinogen bridges between other platelets

### Coagulopathy – Clotting Cascades

- **Clotting factor deficiency**, bleeding from large vessels,
- Sx: hemorrhage, large ecchymosis, bleeding w/ trauma
- **Classic Hemophilia A**: VIII def, XLR, bleeding is variable
  - based on VIII activity, bleed in joints, muscles, subQ
  - **prolonged PTT**: normal values for bleed time, platelets, PT
  - PT correctable in vitro w/ addition of fresh frozen plasma
- **Christmas Disease**: (IX deficiency), XLR, same as classic
- **Vit. K Deficiency**: affects II, VII, IX, X, **prolonged PT/PTT**
  - adults: from fat malabsorption- pancreatic or small bowel
  - neonates: lack of bacteria in GI (not colonized at birth) to synthesize Vitamin K
Coagulopathy: other

- **vWF Disease:** most common hereditary bleeding disorder
  - Prolonged bleed time (adhesion); prolonged PTT (VIII def)
  - vWF binds GPIb on platelets & subendothelial collagen
  - vWF deficiency leads to decreased platelet adhesion to injury and decreased survival time of factor VIII
- **DIC:** consumes platelets & coag factors (esp. II, V, VIII)
  - Microangiopathic hemolytic anemia (schistocytes)
  - Increased PT/PTT, bleed time, fibrin split products
  - From: tissue thromboplastin or activation intrinsic pathway
  - Obstetric complications, infection, cancer, trauma

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Essential Thrombocythemia

- Myeloproliferative disease (like polycythemia vera) confined to megakaryocytes
- Megakaryocytosis in marrow
- Platelet counts >600,000/µL (thrombocytosis) and often abnormally large platelets seen
- Hemorrhage, thrombosis, and erythromelalgia (throbbing/burning of hands and feet) occur.

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Waldenstrom's Macroglobulinemia

- Syndrome in which a lymphoplasmytic lymphoma secretes an excess of IgM immunoglobulins
- Unlike multiple myeloma, characteristically involves spleen and peripheral lymphoid tissues, not bone marrow
- Bone marrow contains a diffuse infiltrate of neoplastic lymphocytes/plasma cells with Russell bodies (PAS immunoglobulin inclusions)
- Hyperviscosity of blood causes neurological symptoms, retinal vein tortuosity, cold agglutinin hemolysis, cryoglobulinemia (Raynaud's)
- Disease of older adults, median survival 4 years

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Multiple Myeloma

- Arises from clonal proliferation of an antibody-producing cell that makes a singular isotype of immunoglobulin, usually IgG or IgA; this is the "M" protein; there is suppression of all other Ig's.
- NOT a true plasma cell; from a B cell precursor
- Causes lytic bone lesions and hypercalcemia/uria.
- Associated with bone pain and pathological fractures.
- Free light chains in the urine are Bence-Jones proteins.
- Anemia, myeloma kidney, amyloidosis, Rouleaux form.
- Does NOT affect liver and spleen
- Death is from renal dysfunction and/or infection.

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Coagulopathy: Other Cont’d

- **Liver disease:** all coagulation factors from liver except vWF
  - Prolonged PT/PTT, thrombin time, Vit. K may help
- Prolonged bleed time from thrombocytopenia OR functional platelet problem (e.g. Glanzman)
- **Dilutional:** multiple transfusions with stored blood that is deficient in factors II, V, VIII
  - May cause thrombocytopenia or prolonged PT or PTT
  - Persistent bleeding from surgical wounds

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MGUS and Solitary Myeloma

- **Monoclonal Gammapathy of Unknown Significance** – 1-3% of elderly have presence of monoclonal immunoglobulin "M" component in blood; no signs, symptoms, or Bence Jones proteinuria…significant in that it rarely will progress to multiple myeloma
- **Solitary myeloma (Plasmacytoma)** – solitary plasma cell neoplasm in bone or soft tissue; progression to multiple myeloma only with some bony lesions; soft tissue lesions can be excised and cured.
Heavy Chain Disease

- Common feature is secretion of immunoglobulin fragments (H, not L, chains) from neoplastic B-cells in leukemias or lymphomas
- Alpha – most common; young people; infiltration of lamina propria of intestine with lymphocytes causes malabsorption.
- Gamma – elderly people; like malignant lymphoma; symptoms of lymphadenopathy, anemia, fever.
- Mu – seen in CLL without lymphadenopathy

Leukemia – General Features

- Malignancy of lymphoid or hematopoietic cell origin
- Number of circulating leukocytes ↑ in blood
- Bone marrow diffusely infiltrated with leukemic cells
  - → encroachment on normal marrow development
  - → Marrow failure with pancytopenia (acute leukemias)
  - → anemia (↓RBCs), infections (↓mature WBCs), hemorrhage (↓platelets)
- Infiltration of leukemic cells in liver, spleen, lymph nodes
  - Acute: blasts in bone marrow and peripheral blood
  - Chronic: mature lymphoid/hematopoietic cells proliferate

ALL-Acute Lymphoblastic Leukemia

- Young children → Most responsive to therapy
- Stormy onset with features of marrow failure
  - →Pallor, petechiae, and purpura
- B-cell Lymphoblasts in marrow and peripheral blood
- Sternal tenderness, BONE PAIN, lymphadenopathy, and hepatosplenomegaly
- Spread to CNS (meningeal), testes
  - CD19, CD20, CD10; Staining for TdT
  - T Cell ALL’s: adolescent male, T cell lymphoblasts, mediastinal lymphoblastic lymphoma, mediastinal mass

AML – Acute Myeloblastic Leukemia

- Accumulation of myeloid blasts in marrow (>20% BLASTS)
  - Pancytopenia
- Young adults (15–29yrs) are primarily affected
- Incidence ↑ w/ age, including blast transformation of chronic CML; median age 65
- Myeloblasts contain myeloperoxidase-positive granules & Auer rods; Monocytic forms may contain non-specific esterases; TdT (terminal deoxytransferase) is negative (present in <5% of cases)
- Variable WBC counts (50% < 10K)
  - rare splenomegaly
- Promyelocytic leukemia (M3)
  - t(15;17) translocation with fusion of the retinoic acid receptor gene and abnormal retinoic acid receptors
  - Tx: all-trans retinoic acid (Vitamin A)

AML – Acute Myeloblastic Leukemia

- Older adults (>60yrs) → most indolent (asymptomatic)
- Absolute lymphocyte counts >4,000
- ↑ in small lymphocytes in peripheral blood (Smudge cells)
- Lymphadenopathy and hepatosplenomegaly
  - Patients have hypogammaglobulinemia and increased susceptibility to bacterial infections
  - Some patients develop warm antibody autoimmune hemolytic anemia or thrombocytopenia
  - (CD19, CD20) + CD5; DO NOT contain TdT or CD10
  - B cells; overlaps with small lymphocytic lymphoma

CLL – Chronic Lymphocytic Leukemia

- Older adults (>60yrs) → most indolent (asymptomatic)
- Absolute lymphocyte counts >4,000
- ↑ in small lymphocytes in peripheral blood (Smudge cells)
- Lymphadenopathy and hepatosplenomegaly
  - Patients have hypogammaglobulinemia and increased susceptibility to bacterial infections
  - Some patients develop warm antibody autoimmune hemolytic anemia or thrombocytopenia
  - (CD19, CD20) + CD5; DO NOT contain TdT or CD10
  - B cells; overlaps with small lymphocytic lymphoma
CML – Chronic Myelogenous Leukemia

- Peak incidence in 30’s – 40’s
- Very high peripheral WBC counts with varied immature forms (>100,000) \(\rightarrow\) myeloid stem cell proliferation
- **Splenomegaly**, extramedullary hematopoiesis
- Nonspecific symptoms: anemia, fatigue, weight loss
- Leukocyte alkaline phosphatase (LAP) is found in normal leukocytes, *but not leukemic cells (very low)*
- **Blast Transformation** (AML or ALL) “Blast crisis”
- Philadelphia chromosome \(t(9;22)\)
  - Uncontrolled tyrosine kinase activity \(\rightarrow\) bcr-c-abl fusion gene product
  - Inhibition of tyrosine kinase may treat

Hairy Cell Leukemia

- Rare B cell neoplasm of middle-aged males
- Morphology:
  - Small leukocytes with fine, hair-like cytoplasmic projections
- Clinical findings:
  - Tartrate resistant acid phophatase (TRAP)
  - Splenomegaly \(\rightarrow\) dragging sensation
  - Pancytopenia from marrow failure \(\rightarrow\) recurrent infections, low WBC count

Non-Hodgkin's Lymphoma – General Features

- NHL = peripheral infiltration and mass formation in lymphatic system with only moderate immune dysfunction.
- Lymphoma begins in lymph nodes and can spread to BM, spleen, liver, etc; leukemia starts as neoplasm of marrow and can spread to lymph nodes, spleen, etc.
- Nontender (painless) lymph node enlargement = malignancy
- Noncontiguous lymph node spread = NHL
- Most NHL are B cell neoplasms (all follicular = B cell)
- All forms of NHL show a destroyed architecture of the node = Effacement

NHL - Staging

- Stage I = single node or extra nodal site
- Stage II = 2 or more lymph node regions on same side of diaphragm (either above OR below) or limited contiguous extralymphatic organ/tissue involved
- Stage III = Involvement of lymph nodes on BOTH SIDES of Diaphragm (includes spread to spleen)
- Stage IV = multiple or disseminated foci with extralymphatic spread (bone marrow/organs
- A = no constitutional symptoms
- B = fever, night sweats, weight loss*

WHO/REAL Classification

<table>
<thead>
<tr>
<th>Neoplastic cell</th>
<th>Morphology</th>
<th>%</th>
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<tbody>
<tr>
<td>CLL/Small cell lymphoma</td>
<td>Small, mature looking lymphocytes</td>
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<tr>
<td>Follicular lymphoma</td>
<td>Small cells with cleaved nuclei</td>
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<tr>
<td>Acute lymphoblastic (T-cell)</td>
<td>Lymphoblasts</td>
<td>15</td>
</tr>
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</table>

Small Cell Lymphocytic/CLL

- (associated w/ chronic leukemia \(\rightarrow\) spectrum of same disease… distinction is site of origin, but histo is the same)
- Bone marrow involved EARLY – CLL
- Generalized lymphadenopathy around age 60 or older, males
- Least necrosis and least effacement of node of all the NHL
  - Fairly normal looking follicular cells
  - Well-differentiated, more hyperplastic than anaplastic
  - Low grade = indolent = not responsive to chemo
- Increased infections secondary to hypogammaglobulinemia (normal immune system is compromised)
- B cells: CD 19 and 20, CD5
Follicular (Nodular) Lymphoma
- B cell, nodular lymphoma,
- #1 type of NHL, aka “small cleaved cell” cleaved, folded nucleus
- Indolent; Age = 50-60, Males=Females
- t(14;18) bcl-2 over-expression=↑anti-apoptotic = follicular lymphoma
- Recapitulation of numerous normal germinal centers with follicles with stromal proliferation
- Less differentiated than small cell, but more well-differentiated than Large cell or Lymphoblastic
- * can progress to high grade (diffuse) NHL without therapy — aggressive subclones
- CD 19 and 20, CD 10+, CD5- w/ high surface IgG

Diffuse Large Cell High Grade Lymphoma
- Rapidly enlarging SINGLE NODE or EXTRANODAL— especially in Waldeyer’s ring of the oropharynx (50%)
- Median age 60, M>F
- 80% B cells, 20% T cells
- Bone marrow is RARELY involved
- Aggressive, but responds to chemo
- Association with previous IMMUNOLOGIC DISORDER: Sjogren’s, Hashimoto’s, AIDS
- B cell derived with large, multilobulated nuclei; “plasmacytoid”
- CD 19 and 20, CD10 but TdT NEGATIVE

Acute Lymphoblastic Lymphoma/ALL
- B cell form (80%) = identical to ALL
  - Young child w/ petechiae, infection
  - Undifferentiated (blasts) = large cells
  - most anaplastic and aggressive of NHL (responds to chemo) – high grade
  - CD19+, CD10+, CD3-, sig-, TdT positive, no peroxidase-positive granules
- Acute Lymphoblastic T-cell Lymphoma
  - males, age < 20
  - like T cell ALL with PROMINENT MEDIASTINAL MASS
  - can lead to vena cava obstruction → SVC syndrome
  - involves Bone Marrow early
  - TdT + with high rate of mitoses (anaplastic)

Burkitt’s Lymphoma
- (small noncleaved cell lymphoma)
- B cell, mostly in kids and young adults (M>F)
- High mitotic index (40%)
- t(8;14) – c-myc gene moves next to heavy chain Ig gene
- African form = aggressive, invasive lymphoma of jaw; associated with EBV; aggressive, so it responds well to chemo
- In U.S., it presents as an abdominal lymphoid mass
- “Starry Sky” Appearance on LM with light histiocytes dotting a field of dark purple lymphocytes

Mycosis Fungoides/Sezary Syndrome
- Tumor of peripheral CD4+ T cells, indolent
- CD3, CD4 normal T cell markers
- Mycosis Fungoides
  - Cutaneous T cell lymphoma w/ infiltration of epidermis/upper dermis with neoplastic T cells (infolded nuclear membranes)
  - Pautrier’s microabscesses (malignant T cells)
  - Uricarial skin lesions (NOT a fungus)
- Sezary Syndrome
  - Less cutaneous involvement with more leukemia (BLOOD) association
  - Sezary cell = “convoluted nucleus”
  - PAS + T cells are present in blood

Adult T cell Lymphoma/Leukemia
- T cell neoplasm caused by the HTLV-1 retrovirus, endemic to Japan and the Caribbean; STD
- Presentation:
  - Skin lesions, generalized lymphadenopathy, hepatosplenomegaly
  - Hypercalcemia- associated w/ lytic bone lesions
  - ↑ lymphocyte count w/ multilobulated CD4+ cells
  - * extremely AGGRESSIVE disease with mean survival of only 5 months!
### Hodgkin’s Disease

<table>
<thead>
<tr>
<th>Hodgkin’s Disease</th>
<th>Non-Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed-Sternberg cell</td>
<td>characteristic</td>
</tr>
<tr>
<td>Inflammatory cell component</td>
<td>present</td>
</tr>
<tr>
<td>Cell population</td>
<td>polymorphic</td>
</tr>
<tr>
<td>Nodal distribution</td>
<td>localized, single axial group</td>
</tr>
<tr>
<td>Type of nodal spread</td>
<td>contiguous</td>
</tr>
<tr>
<td>Mesenteric nodes and Waldeyer’s ring</td>
<td>no</td>
</tr>
<tr>
<td>Extranodal involvement</td>
<td>no</td>
</tr>
<tr>
<td>Prognosis</td>
<td>80% cure</td>
</tr>
<tr>
<td>Age at onset</td>
<td>young, &lt;30</td>
</tr>
</tbody>
</table>

**Hodgkin’s Disease**

- characterized by presence of **Reed-Sternberg cells** which are required, but not sufficient for the diagnosis
  - Large multinucleated or one nucleus with multiple lobes, each with large inclusion-like nucleolus
  - Almost all are B-cell origin
- has an **inflammatory cell component**
- extranodal involvement **rare** and **rare involvement** of Mesenteric nodes and Waldeyer’s ring
- **Constitutional signs and symptoms** (*B* symptoms); low grade fever, night sweats, and weight loss.
- **Young Adults** with mean age 32. 50% of cases are associated with EBV

### Nodular Sclerosis Hodgkin’s Disease

- **most common form** (65-75%); adolescents or young adults; F = M
- lower cervical, supraclavicular, and mediastinal nodes
- **Lacunar cell variant of RS cell and collagen bands** that divide the lymphoid tissue into circumscribed nodules; **few classic RS cells**
  - CD15+/CD30+ RS cells
- **Background**: reactive inflammatory infiltrate includes lymphocytes, eosinophils and plasma cells.
- Prognosis is **excellent** but depends on the stage

### Mixed Cellularity Hodgkin’s Disease

- **second most common form** (25%); more common in males
- **Numerous classic RS cells**.
- Background includes lymphocytes, plasma cells, eosinophils, and histiocytes; Less Lymphocytes
- **Diffuse EFFACEMENT of lymph nodes**; necrosis and fibrosis
- Usually **disseminated** disease at presentation with systemic manifestations
- Prognosis: **Intermediate**

### Lymphocyte Predominant Hodgkin’s Dis.

- uncommon variant (6%); **majority < 35 year old males**
- Resembles nodular NHL; nodular like infiltrate of mature lymphocytes with variable numbers of histiocytes and a paucity of RS cells; the transformed cell is a B-cell (CD20+, CD30-, CD15-)
- **(L+H popcorn RS cell)** – pale cell with multilobed nucleus
- No association with EBV
- **excellent prognosis**

### Lymphocyte Depleted Hodgkin’s Disease

- least common form (rare); **older males** with disseminated disease
- **paucity of lymphocytes and abundance of RS cells**
  - (RS high relative to lymphocytes)
- present with systemic manifestations, disseminated involvement, and have aggressive disease
- Associated with EBV in majority of cases; common in persons with HIV infection
- **Poor prognosis**