Pathology Review Flash Cards
General Pathology
Spring 2009

Cell Adaptation
• Causes
  – Increased/decreased demand or workload
  – trophic stimulation (ex: hormones, growth factors)
  – decreased nutrients/ischemia/denervation
  – chronic irritation/inflammation
• Types
  – hyperplasia
  – hypertrophy
  – atrophy
  – metaplasia

Cell Adaptation
• Hypertrophy = (+) cell volume
  – Due to increased synthesis of structural components
  – Caused by increased functional demand (ex: skeletal muscle) or hormonal stimulation (ex: breast tissue during lactation)
• Hyperplasia = (+) cell number
  – Occurs if cell population is capable of synthesizing DNA
  – Physiologic – Ex: female breast at puberty (hormonal) or liver regrowth after partial hepactectomy (compensatory)
  – Pathologic – excessive hormones/growth factors (Ex: endometrium)
    • Can lead to cancerous proliferation
• Both – Triggered by same mechanism
  – Ex: Estrogen-induced growth of pregnant uterus

Cell Adaptation
• Atrophy = shrinkage due to loss of cell substance
  – Physiologic – Ex: fetal developmental atrophy of notochord or thyroglossal duct
  – Pathologic – Can be local or generalized
  – Causes:
    • decreased workload (broken limb in cast)
    • decreased nutrition (cachexia)
    • aging (senile atrophy) of brain/heart
    • pressure/ischemia (benign tumors)
    • loss of nerve or endocrine stimulation (menopause shrinks the breasts)

Cell Adaptation
• Metaplasia – reversible change in which one adult cell type is replaced by another adult cell type
  – Caused by changes in cytokines, growth factors, and ECM components in surrounding environment
  – Ex: Columnar to squamous- occurs in trachea and bronchioles of smokers or in Vit A deficiency
  – Squamous to columnar- Barrett’s esophagus, due to chronic acid exposure
• Influences that predispose to metaplasia may induce cancer formation if the stimulus persists

Cell Injury and Necrosis
• Common Biochemical Mechanisms of Cell Injury
  – ATP depletion: loss of ATP-dependent processes → inability to maintain ion gradients due to loss of Na⁺/K⁺ pump function;
    • increased Na⁺ in cell leads to cell swelling and dilation of endoplasmic reticulum
  – Mitochondrial damage: will ultimately kill cell; increased Ca²⁺ in cytosol causes formation of high conductance channels (“mitochondrial permeability transition”)
    • non-selective pores form, interfering with membrane function
    – Oxidative phosphorylation lost
  – Disturbance of Ca²⁺ homeostasis: both influx and release from intracellular stores (loss of sequestration in mitochondria and ER)
    • activation of enzymes (phospholipases, endonucleases, etc.)
    • increased mitochondrial permeability leading to apoptosis
Cell Injury and Necrosis

- **Common Biochemical Mechanisms of Cell Injury**
  - **Damage from free radical accumulation**: often from toxins and environmental agents; 3 mechanisms:
    - **Lipid peroxidation of membranes** (both in cell and mitochondria)
    - Oxidative modification of proteins
    - **Formation of thymidine dimers, DNA strand disruption**
  - Normally, free radicals removed from cells by catalase, superoxide dismutase, antioxidants, and scavengers
  - **Defects in cell membrane permeability**: decreased phospholipid synthesis from mitochondrial dysfunction and activation of lipases due to increased Ca²⁺ in cytosol cause damage to cell membranes

- **Specific Routes of Cell injury**
  - **Hypoxia**: caused by ischemia (most common), low oxygen tension, CO poisoning, severe anemia
    - Cell unable to perform oxidative phosphorylation (first change), switches to anaerobic glycolysis
    - Results in buildup of lactic acid, activation of lysosomal enzymes
  - **Reperfusion injury**: re-establishment of blood flow to an ischemic area can actually enhance damage
    - Mediated by oxygen free radicals produced from metabolic pathways and inflammatory cells that come into damaged tissue
    - Hallmark sign is *contraction bands* seen on microscopy

- **Chemical injury**: CCl₄ forms highly reactive free radical CCl₃; damage to membrane fatty acids and apoproteins necessary for lipid export in liver
  - Fatty liver results
  - Acetaminophen causes similar damage mediated by free radicals and toxic metabolites; see peroxidation of lipids in membranes

- **Cell Degeneration and Reversible Cell Injury**
  - Cytoplasmic vacuolization
    - Endoplasmic reticulum fills with H₂O, segments pinch off forming vacuoles
    - In fatty change, these vacuoles are filled with lipids
      - "Ballooning degeneration"
    - Extensive swelling and vacuolization of cells prior to disruption
    - Cytoplasm has eosinophilic appearance

- **Coagulative Necrosis**
  - **Microscopic**
    - Nucleus is absent or karyorrhectic
    - Cytoplasm is eosinophilic
      - Loss of cytoplasmic RNA
    - Basic structural outline of the cell is preserved
  - **Gross**
    - Tissue architecture is preserved
  - **Mechanism**
    - Intracellular acidosis denatures structural proteins and proteolytic enzymes so autolysis is minimized
    - Result of hypoxia – except in brain
Liquefactive Necrosis

- **Microscopic**
  - Infiltration by neutrophils
  - Fibrous connective tissue surround older lesions
  - Tissue architecture destroyed
- **Gross**
  - Soft to liquefied viscous mass
  - Insipissated material
- **Mechanism**
  - Pyogenic bacteria stimulate inflammatory response
  - Neutrophils release proteolytic enzymes
  - Hypoxia in CNS

Calcification

- **Dystrophic**
  - Calcium deposited locally in necrotic tissue
    - Basophilic, amorphous granular or clumped
    - Can be intracellular, extracellular or both
  - Normal serum levels and metabolism
  - Found in advanced atherosclerotic plaques
  - Psammoma body formation

Calcification

- **Metastatic**
  - Deposition of calcium phosphate in normal tissue
  - hypercalcemia
  - Increased parathyroid hormone secretion
  - vit. D toxicosis
  - tumors associated with increased bone catabolism
    - multiple myeloma
  - Renal osteodystrophy – secondary hyperparathyroidism

Lipofuscin

- Insoluble, wear and tear pigment
  - Does not harm cell or cellular functions
- End product of membrane lipid peroxidation
- Commonly accumulates in the elderly
  - Most often in hepatocytes and myocardium
- Combination of lipofuscin accumulation and atrophy of organs is brown atrophy

Apoptosis - Intro

- Process of programmed cell death
- Several different initiating events but each ultimately results in activation of caspases that degrade nuclear and cytoskeletal elements
  - Caspases exist aszymogens that must undergo cleavage to be activated
  - Caspases degrade nuclear and cytoskeletal scaffold
  - Caspases activate DNAse which degrade nuclear DNA
- Plasma membrane remains intact and cellular contents do not leak out
- Apoptotic cells recognized and phagocytosed
- **No inflammatory response**

Apoptosis vs. Necrosis

<table>
<thead>
<tr>
<th>Apoptosis</th>
<th>Necrosis</th>
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<tbody>
<tr>
<td>fragmentation without extrusion of contents</td>
<td>dissolution of the cell with extrusion of contents</td>
</tr>
<tr>
<td>Phagocytosis of fragments but no inflammatory response</td>
<td>necrosis stimulates a local acute inflammatory response</td>
</tr>
<tr>
<td>No cell loss apparent</td>
<td>Loss of tissue and architecture</td>
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</table>
Causes of Apoptosis

<table>
<thead>
<tr>
<th>Physiologic</th>
<th>Pathologic</th>
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<tbody>
<tr>
<td>Embryogenesis</td>
<td>Viral infection</td>
</tr>
<tr>
<td>Clonal deletion</td>
<td>Secondary to obstruction</td>
</tr>
<tr>
<td>Hormone-dependent processes</td>
<td>Secondary to hypoxia</td>
</tr>
<tr>
<td><strong>degeneration of uterine lining</strong></td>
<td></td>
</tr>
<tr>
<td>Maintenance of rapidly proliferating cell populations</td>
<td>Heat, radiation</td>
</tr>
<tr>
<td>Cytotoxic T cells</td>
<td>Cytotoxic drugs</td>
</tr>
<tr>
<td>Immune modulation by cytokines</td>
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Apoptosis – Mechanisms

- **Extrinsic pathway (death-receptor)**
  - Initiated by TNF family receptors engaging Fas ligand (FasL or CD95L)
  - Fas – FasL interaction causes cytoplasmic death domains to come together and form binding site for FADD (Fas-associated death domain)
  - FADD binds inactive form of caspase-8
  - Multiple pro-caspase-8 molecules brought together and cleave one another to active caspase-8
  - Cascade of executioner caspases triggered and results in apoptosis

- **Intrinsic pathway (mitochondrial)**
  - Occurs as a result of growth factor and/or hormone deprivation
  - Anti-apoptotic proteins (Bcl-2 family) are lost from mitochondrial membrane and replaced by pro-apoptotic members
  - Change in ratio of anti-apoptotic to pro-apoptotic proteins leads to increased mitochondrial permeability
  - Cytochrome c leaks out and activates caspases

- **DNA damage mediated**
  - Caused by radiation, toxins, or free radicals
  - DNA damage leads to accumulation of p53
  - p53 results in:
    - Caspase activation
    - Bcl-2 family changes that result in caspase activation
    - Loss of p53 results in decreased apoptosis and growth of a mutated cell

- **Cytotoxic T cell mediated**
  - Cytotoxic T cells recognize foreign antigens on infected host cells
  - Perforin secreted and forms pore in membrane that allows entry of granzyme B
  - Granzyme B activates caspases

Apoptosis – Morphology

- Involves single cells or small clusters of cells
  - Intensely eosinophilic cytoplasm and dense nuclei
- Cell shrinkage
- Chromatin condensation
  - Nuclear fragments with chromatin aggregated peripherally
  - DNA demonstrates ladder pattern on electrophoresis due to enzymatic cleavage into 200 base pair fragments
- Cytoplasmic blebs / apoptotic bodies
  - Membrane bound bodies of cytoplasm
  - Tightly packed organelles
  - +/- nuclear fragments
- Phagocytosis of apoptotic bodies
  - Expression of new cell membrane ligands which have been flipped out from the inner layers
  - Allows for recognition for uptake by phagocytes

Accumulations

- **Fatty Change**
  - Hypoxic, toxic, or metabolic injury
    - Most commonly in liver but also myocardium, muscle and kidney
    - Associated with alcohol, diabetes, obesity, protein malnutrition, CCl4, Reye’s syndrome
  - Dispersion of ribosomes or damage by free radicals/Ca++
    - Decreased protein synthesis resulting in decreased synthesis of lipid acceptor protein, decreased extracellular lipid transport and intracellular (intracytoplasmic) accumulation of triglycerides
  - Morphology:
    - Gross lesions: greasy, yellow, enlarged liver
    - Microscopic lesions: intracytoplasmic vacuoles that stain orange/red with Sudan IV or Oil Red-O
Accumulations

- Protein accumulations (non-specific, eosinophilic)
  - eosinophilic intracell deposits = hyaline change
  - examples: proximal renal tubules (proteinuria), Russell bodies (accumulation of Ig in ER of plasma cells), Mallory bodies (cirrhosis), α-1 antitrypsin deficiency, α-synuclein/Lewey Bodies (familial/sporadic Alzheimer’s, PD, dementia)

- Glycogen
  - Non-staining cytoplasmic vacuoles assoc. w/ abnl glucose/glycogen metabolism (DM: hepatocytes/renal tubules; glycogen storage disease)

Hemosiderin, Ferritin, Fenton Reaction

- Hemosiderin- intracellular insoluble degradation product of iron
  - Formed by ferritin when there is excess of iron

- Ferritin is an iron-protein complex found in all cells
  - when measured in the plasma it is a major indicator of iron load

- Fenton reaction- Production of free radicals that contribute to cell injury
  - \( \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^- \)

Inflammation overview: Cardinal signs

- Rubor: redness- dilation of vessels & incr. permeability
- Dolor: pain-incr. pressure from interstitial fluid & bradykinin or other mediators
- Calor: heat-from increased blood flow
- Tumor: swelling-from extravascular accumulation of fluid related to increased vascular permeability
- Functio laesa: loss of function-often related to pain or swelling that makes use of inflamed tissue difficult
- Causes: infection, trauma, chemical injury, immune injury physical injury (heat, radiation), tissue death

Inflammation overview: evolution Timeline

- sec-min: initiation of cascade & hemostasis—His, 5HT
  - amplification-hageman factor, complement, kinins, coag

- min-hrs: reflex vasoconstriction then vasodilation
  - axonal reflex PGs His—congestion/dilation
  - incr. vasc. perm-His, C5a, C3a, Kinins, PGs—edema

- hrs-days: activation/migration of cells—LTs, PGs, cytokines
  - emigration of cells-neutrophils, monos, lymphos

- days: phagocytosis-cytokines, PGs,-necrosis/infiltrate

- days-wks: clear/prolif-growth factors-granulation tissue/fibrosis

Inflammation Overview: Delivery of cells

- Vasoactive: vasoconstriction followed by dilation
  - leads to increased blood flow—redness warmth

- Incr. Cap. perm: His, 5HT: leak protein & fluid - edema
  - from endothelial contraction (gaps) in postcap. venules

- Adhesion: to draw inflammatory cells to injury site
  - Integrin: LFA-1 etc on WBCs bind endothelial ICAMs etc
  - Immunoglobulin-family adhesions: on endothelium
  - bind integrins on WBCs, ICAM-1, ICAM-1, VCAM
  - Selectins: induced by IL-1 & TNF; L on neutro bind endo

- E & P on endo, bind sialyl-Lewis X on WBCs

Inflammation Overview: Phagocytosis

- Ingest material by phagocytes-neutros/monos/macros
  - opsonized particle internalized in phagosome that fuses
  - w/lysosome to form phagolysosome—WBC degranulates

- Opsonization: coating particle by opsonins to immobilize
  - IgG & C3b are examples of opsonins
  - IgG binds fragments, WBCs bind Fc portion of IgG
  - C3b binds fragments, WBCs bind C3b also

- Microbial Killing: O2 dependent or independent
  - O2 dependent: most important, uses NADPH oxidase in phagosome to produce ROS-destroy proteins/microbe wall
Types of Inflammation

- **Classification by Duration**
  - Chronic - weeks to years
    - Usually from persistence of injury-causing agent
    - Infection, autoimmune disease, sterile agent
    - Monocytes and macrophages
    - Also lymphocytes, plasma cells, eosinophils
    - Necrosis NOT as prominent as in acute inflammation
    - Loss of parenchyma due to fibrosis
    - Granulation tissue converted to scar tissue
    - Blood vessel proliferation
    - Granuloma - type of chronic inflammation

- **Classification by Morphologic Type**
  - Serous
    - Lack of cellular infiltrate
    - Accumulation of fluid from blood serum due to increased vascular permeability
    - From mesothelium - pleural, peritoneal, pericardial
  - Fibrinous
    - Increased vascular permeability allows for passage of fibrin exudate
    - Gives a "shaggy" appearance
    - Resolves via lysis - degradation by plasmin and macrophages
    - Organization - fibrin remains, involved in fibrosis and scarring
  - Suppurative
  - Granulomatous

Inflammation overview:

**WBC emigration**

- **Emigration**: process of WBC migration from post capillary venule, between endothelial cells, and into tissue
- **Margination**: blood slowing, movement of WBCs to vessel periphery
- **Adhesion**: mediated by sequential expression of specific surface molecules
  - **Weak adhesion**: between endothelial selectins and WBC surface carbohydrates, results in "rolling"
  - **Firm Adhesion**: between endothelial ICAM/VCAM and WBC integrins
  - Sequential expression of different CAMs determines what type of WBC migrates at different phases of inflammation (PMN, mono, etc)
- **Transmigration**: WBC "pseudopod" formation, diapedesis by "crawling" along ECM

Adhesion molecules

<table>
<thead>
<tr>
<th>selectin</th>
<th>sugars</th>
<th>Weak adhesion</th>
<th>P-selectin, E-selectin - Neutrophil rolling</th>
</tr>
</thead>
<tbody>
<tr>
<td>integrin</td>
<td>Ig family</td>
<td>Firm adhesion</td>
<td>ICAM-1 (endothelial cell): LFA-1 integrin (PMN)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VCAM (endothelial cell): VLA4 integrin (monocyte)</td>
</tr>
</tbody>
</table>
Inflammation Overview: Chemotaxis

- Process of WBC attraction & movement to specific site
- Requires gradient of chemotactic factors
  - bacterial products, complement, cytokines, leukotrienes, kalikrein, eosinophilic chemotactic factor
  - complement (C5a), LTB4, IL-8: for PMNs
- Chemokines activate cell receptors w/ release of second messengers and Calcium
- Cytoskeletal polymerization & contraction of side of cell with greatest chemokine concentration → migration

Plasma Proteins in Inflammation

- Kinins
  - play a role in inflammation, blood pressure control, pain, and coagulation
  - During acute inflammation, bradykinin contributes to hyperalgesia
  - Bradykinin also triggers vasodilation, increases vascular permeability, and causes smooth muscle contraction
- Complement
  - Anaphylatoxins – C3a, C4a, C5a
  - C5a also chemotactic for neutrophils
  - C3b opsonizes bacteria
- Hageman factor – serine protease; activates other mediators
- Products of fibrinolysis (fibrinopeptides)

Leukotrienes, Prostaglandins

- Synthesized from arachidonic acid in activated cells
  - Arachidonic acid released from membranes by phospholipase activation
    - Phospholipase C – acts on diacyl glycerol (DAG)
    - Phospholipase A2 – acts directly on phospholipids
- Type of eicosanoid formed depends on specific enzymes in cells
  - Macrophages: cyclooxygenase – PGE, PGF
  - Neutrophils: lipoxygenase – LTB4
  - Mast cells: lipoxygenase – LTC, LTD, LTE

Leukotrienes, Prostaglandins

- LTC4, D4, E4: vasoconstriction, bronchospasm, and increased vascular permeability (SRS-A's)
- LTB4: neutrophil chemotaxis and adhesion
- PGD2 (mast cells): vasodilation, edema
- PGE2: vasodilation, hyperalgesia, fever
- PGF2 (prostacyclin): vasodilation, inhibits platelet aggregation
- TXA2: antagonizes prostacyclin (causes platelet aggregation, vasoconstriction)
- COX-1: kidneys, stomach
- COX-2: inflammation

IL-1, TNF-a, and IL-6

- Synthesized by activated macrophages
- Overlapping functions
- Local activation of endothelial cells
  - increased vascular permeability, adhesion molecules, cytokine and growth factor synthesis
- Acute-phase (systemic)
  - fever- endogenous pyrogens
  - increase in acute phase proteins
  - Leukocytosis- increased release, delivery, cytokine production
  - Results in early release of neutrophils (bands)
- Also cause lymphadenitis and malaise
- Fibroblast proliferation and collagen synthesis

IL-1, TNF-a, and IL-6

- IL-1
  - synthesized as larger molecule then cleaved into 2 homologous forms
  - Involved in tissue repair
- TNF-α
  - activates death domain (TNF-R1, TRADD signaling
  - monoclonal antibody to TNF- used to treat inflammatory conditions (RA & Crohn’s)
- IL-6
  - local production causes increased osteoclast activity and bone loss (inhibitors- tx osteoporosis)
Chemokines
• Produced locally to mediate chemotaxis of specific cell types; seven-spanning transmembrane receptors linked to G proteins
• Similar structure with 70-80 aa residues and 2 conserved cysteines
• Adjacent- C-C; aa separating- C-X-C
• CXC8 (=IL-8): chemotactic for neutrophils (acute inflammation); made by MACROPHAGES and endothelial cells
• MCP-1- chemotactic for monocytes; made by MACROPHAGES induces histamine release from mast cells
• RANTES/MIP-1- chemotactic for eosinophils (allergic response)

Chemokines Receptors and Disease
• 7 spanning G protein linked receptors
• CXCL8’s receptor is CXCR1
• CXCR4 and CCR5 act as HIV coreceptors- early in disease: monotropic (CCR5), later T-cell tropic (CXCR4)
• Due to their role in inflammation and immunity, agents that inhibit chemokine function are useful to treat disease

Inflammatory Cytokines & Interferons

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Made by</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1, TNFα, IL-6</td>
<td>macrophages</td>
<td>activate inflammatory cells, increase adhesion molecules, vasodilation, vascular permeability, synth of acute phase proteins, regulate fever</td>
</tr>
<tr>
<td>IL-2</td>
<td>T cells</td>
<td>T cell growth factor, autocrine stimulation</td>
</tr>
<tr>
<td>IL-3</td>
<td>T cells</td>
<td>stimulates hematopoietic cells</td>
</tr>
<tr>
<td>IL-4</td>
<td>T cells</td>
<td>stimulates eosinophils, mast cells, IgE production</td>
</tr>
<tr>
<td>IL-5</td>
<td>T cells</td>
<td>stimulates eosinophils, IgA production</td>
</tr>
<tr>
<td>IFN α, β</td>
<td>Antiviral (block viral replication, increase MHC I exp, activate NK cells)</td>
<td></td>
</tr>
<tr>
<td>FN gamma</td>
<td>T and NK cells</td>
<td>activate macrophages (ie in granuloma formation)</td>
</tr>
<tr>
<td>IL-4, 5, 10, 13</td>
<td>TH2 pathway mediators</td>
<td></td>
</tr>
<tr>
<td>IL-12, 18</td>
<td>TH1 pathway mediators</td>
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Growth Factors
• GM-CSF/G-CSF/M-CSF- promotes differentiation of granulocytes in bone marrow; stimulates neutrophils, eosinophils, and monocytes/macrophages
• FGF/TNFα-stimulates fibroblasts in healing and regeneration; fibrosis in chronic inflammation
• Angiogenic factors- FGF, VEGF, PDGF

Inflammatory Therapy
• **Aspirin** – *Irreversibly* inhibits (acylates) cyclooxygenase (Cox 1 & 2)
  • low dose inhibits thromboxane (TXA) synthesis, ↓ platelet aggregation
  • high dose also inhibits prostacyclin (PGI), an inhibitor of platelet aggregation, negating anti-platelet effects
  • Use: antipyretic, analgesic, anti-inflammatory, anti-platelet
  • Side effects: gastric ulcer, bleeding, tinnitus, Reye syndrome
• **Other NSAIDs** (naproxen, indomethacin, ibuprofen)
  • similar mechanism to aspirin, but inhibition is reversible
  • may have less GI irritation, but more nephrototoxic
  • Indomethacin used to close PDAs / PGE keeps PDAs open
• **Acetaminophen**
  • Reversibly inhibits cyclooxygenase (Cox 3) in the CNS
  • Use: antipyretic, analgesic, lacks anti-inflammatory properties
  • Overdose: hepatic necrosis due to glutathione depletion and accumulation of toxic metabolites, occurs in 2-3 days
• **Corticosteroids**
  • inhibit NF-κB-mediated synthesis of cytokins; also phospholipases, blocking all known pathways of eicosanoid metabolism
  • Use: Anti-inflammatory, chemotherapy, immunosuppression
  • Side effects: Cushing-like symptoms, osteoporosis
Inflammatory Therapy

- **Epinephrine**
  - Acts as an \(\alpha\) and \(\beta\) agonist. \(\beta_2\) activates adenylate cyclase in the bronchial smooth muscle, \(\alpha_1\) increases IP3 in vascular smooth muscle
  - \(\uparrow\) cAMP \(\rightarrow\) bronchodilation, countering the histamine \(H_1\), induced bronchoconstriction
  - \(\uparrow\) IP3 \(\rightarrow\) vasoconstriction, countering histamine induced increase in vascular permeability and vasoconstriction
  - \(\beta\) induced \(\uparrow\) in cAMP inhibits mast cell degranulation
  - Uses – anaphylaxis, hypotension

- **Anti-cytokine Antibodies**
  - Anti-TNF antibody (adalimumab, infliximab) & recombinant TNF receptor attached to IgG (etanercept)
  - Used for Crohn’s, rheumatoid arthritis, psoriasis
  - Side effects: infection, reactivation of latent TB
  - Anti-alpha integrin antibody (natalizumab)
  - Used for Crohn’s and multiple sclerosis

- **Antileukotrienes**
  - Zafirlukast, montelukast - block leukotriene receptors
  - Zileuton – inhibits 5-lipoxygenase (blocks conversion of arachidonic acid into leukotrienes)
  - Uses: asthma

Systemic Inflammation - Hyperthermia

- Thermoregulation center is in the hypothalamus
- **Nonpyrogenic Fever:**
  - The "set-point" is normal/unchanged
  - Due to insufficient heat loss or thermoregulation malfunction (Heat Stroke, Malignant Hyperthermia)
- **Pyrogenic Fever:**
  - Due to infection, inflammation, cancer or drugs
  - Exogenous pyrogens stimulate prostaglandin formation in the vascular and perivascular cells of the hypothalamus
  - Endogenous pyrogens IL-1/TNF/IL-6 also stimulate Enzymes that increase prostaglandin synthesis (inhibited by acetaminophen)
  - PG and Arachadonic Acid Products in hypothalamus \(\uparrow\) "set-point"
  - \(>105.8^\circ\text{F} (41^\circ\text{C})\): “life-threatening”

Systemic Inflammation – Forms of Inflammatory Shock (I)

- **Endotoxic/Septic:**
  - LPS (endotoxin) activation of TLR-4
  - Activation of macrophages with production of IL-1, TNF (TLR-4); activation of endothelial cells by IL-6 and IL-8
  - Systemic increased vascular permeability with decreased intravascular volumes
  - ARDS: caused by neutrophil mediated endothelial injury
  - DIC: LPS and TNF activate tissue factor and decrease expression of its inhibitor and thrombomodulin
  - Septic Shock = Triad of DIC, hypoglycemia, and Cardiovascular failure

Systemic Inflammation – Forms of Inflammatory Shock (II)

- **Vascular Leak Syndrome:**
  - Result of chemotherapeutics (interferon/IL-1)
  - Characterized by an increase in vascular permeability accompanied by extravasation of fluids and proteins resulting in interstitial edema and organ failure
  - Leads to fever, edema, pulm. congestion
- **Anaphylactic Shock**
  - Initiated by general IgE mediated hypersensitivity response
  - Associated with Systemic Vasodilation and widespread vascular permeability
  - Results in Shock and Edema
  - Hypotension, tissue hypoperfusion, and cellular anoxia

Systemic Inflammation – Inflammation Terms

- **Lymphadenitis:** inflammation of the lymph nodes
- **Lymphangitis:** 2° inflammation of L. channels, red streaks
- **Leukocytosis:** increase in the number of leukocytes (15-20K+), \(\sim\) a left shift \(\sim\) an increase in the number of bands
- **Leukemoid reaction:** an extreme elevation in the number of leukocytes (40,000+)
- **Leukopenia:** a decrease in the number of circulating leukocytes. Occurs in typhoid, rickettsia, some viral/protozoa
- **Acute Phase Proteins:** Are plasma proteins mainly synthesized by the liver
  - Plasma concentrations increase in response to inflammatory stimuli
  - Include: C-reactive protein, fibrinogen/FI (\%ESR, rouleaux), Serum amyloid A (secondary amyloidosis, replaces apoA in HDL)
### Systemic Inflammation – Inhibitors of Inflammation

- **Glucocorticoids**- synthesized from cholesterol.
  - Suppress the release of arachidonic acid from phospholipids by inhibiting phospholipase A2.
  - Inhibit activation of inflammatory mediator synthesis by NFkB pathway.
- **NSAIDs** inhibit the synthesis of eicosanoids from arachidonic acid primarily by inhibiting the enzyme cyclooxygenase (COX) which is responsible for the first step of prostaglandin synthesis. Aspirin is the only irreversible inhibitor.
  - Cox-1 expressed in most tissues
  - Cox-2 Found in inflammatory cells
  - Cox-3 Found in the brain

### Healing and Regeneration

- **Cell Proliferation (cont.)**
  - Fibroblast growth factors (FGFs): promote the synthesis of extracellular matrix protein by fibroblasts, endothelial cells, monocytes, and other cells.
  - Transforming growth factors (TGFs): TGF-α functions similarly to EGF. TGF-β is a growth inhibitor for many cell types and may aid in modulation the repair process; it is also a chemotactic factor for macrophages and fibroblasts.
  - Macrophage-derived growth factors (IL-1 and TNF): promote the proliferation of fibroblasts, smooth muscle cells, and endothelial cells.

### Healing and Regeneration

- **Absolute requirements:**
  - Relatively intact connective tissue infrastructure
  - Replicative capacity of remaining cells
- **Labile cells:** Actively dividing; capable of regeneration: Most forms of epithelium (basal cells), Bone marrow (stem cells).
- **Stable cells:** Capable of division; capable of regeneration: Parenchyma (eg. hepatocytes), Stroma (eg. fibroblasts)
- **Permanent cells:** Incapable of division and regeneration: Neurons, Myocardial cells

### Healing and Regeneration

- **Cell proliferation: mediated by growth factors**
  - Growth factor receptors are transmembrane proteins that respond to ligand interaction by conformational changes that induce tyrosine kinase activity in their intracellular domains.
  - Platelet-derived growth factor (PDGF):
    - Synthesized by platelets and several other cells.
    - Chemotactic for fibroblasts, smooth muscle cells, monocytes
  - **Epidermal growth factor (EGF):**
    - Promotes the growth of fibroblasts, endothelial cells, and epithelial cells

### Healing and Regeneration

- **Removal of debris:**
  - Early stages of inflammation
  - Liquefaction and removal of dead cellular material, debris.
  - Mediated by neutrophils and macrophages
- **Formation of granulation tissue:**
  - Highly vascular, newly formed connective tissue
  - Fills defects created by liquefaction of cellular debris
  - Mediated by migrating fibroblasts and endothelial cells
- **Scarring:**
  - Amount of collagen in granulation tissue progressively increases
  - Progressive contraction of the wound
  - Mediated by fibroblasts

### Type I Hypersensitivity

- Rapid immunological reaction caused by widespread mast cell degranulation typically mediated by an Ig-E response to antigen
- **Sensitization:** primary exposure results in the antigen being processed by macrophages and dendritic cells. These interact with CD4 TH2 cells and cause the release of IL-4 and IL-5, resulting in production of IgE and eosinophils. The allergen-specific IgE then binds to Fc receptors on the surface of mast cells and basophils.
- Subsequent exposure to the antigen will then lead to crosslinking of IgE which stimulates mast cell degranulation and the release of histamine.
- Mast cells can also degranulate in response to non antigenic stimuli such as NSAIDs, cold, trauma, or exercise
Type I Hypersensitivity
- **Acute phase (within minutes)** - Histamine release causes:
  - Increase in vascular permeability, smooth muscle constriction in the airways, and vasodilation. Production of ECF (eosinophil chemotactic factor) causes recruitment of eosinophils at the site of reaction.
- **Late phase (hours, lasting for days)** - Cross-linking also induces mast cells to synthesize and release prostaglandins and leukotrienes (SRS-A, LTB4, and TNF). These enhance and prolong the inflammation and recruit neutrophils and eosinophils.
- Atopy - the genetic predisposition to formation of IgE in response to antigenic challenge. Thought to be an imbalance between IgE and IgG/IgA production.
- Higher doses of antigen exposure are thought to shift away from IgE production and toward IgG production (theory behind allergy shots)

Type I Hypersensitivity - Clinical Presentation
- Respiratory exposure can cause rhinitis, and asthma
- Skin reactions with allergen will cause hives (urticaria) and eczema
- Hives and urticaria can be caused by systemic distribution of drugs
- Systemic delivery can cause anaphylaxis. A response mediated by blood borne allergens including peanuts, shellfish, drugs, arthropod venoms which causes angioedema, bronchospams, peripheral vasodilatation, or N/V/D. Severe episodes can lead to fatal shock.
- Tx of type I hypersensitivity - H1 antagonists, epinephrine (anaphylaxis), corticosteroids (to prevent late phase asthma)

Type II Hypersensitivity
- **Antibody mediated disorders**
  - Antibodies to antigens on cell surface or ECM
  - 3 mechanisms:
    - Opsonize cells or activate complement
    - Antibodies bind ECM and recruit neutrophils and macrophages that cause inflammation and tissue damage
    - Antibodies bind normal cellular receptors and interfere with functioning (e.g. myasthenia gravis, Graves)
- **Pathological Lesions**: Cell Lysis and Inflammation
- **Prototype Disorder**: Goodpasture’s syndrome and Autoimmune Hemolytic anemia

Type III Hypersensitivity
- **Immune Complex Mediated**
  - Antigen combines with antibody in the circulation and is then deposited, or complexes form at an extravascular site where the antigen has been deposited
  - Inflammation occurs at the site of deposition by activating complement, neutrophils, and macrophages
  - **Associated with hypocomplementemia**
  - Examples
    - serum sickness (systemic): 5-10 days after exposure; fever, urticaria, arthralgias, proteinuria, lymphadenopathy
    - Arthus reaction (local): localized tissue necrosis from acute vasculitis due to immune complexes in the skin; peaks after 4-10 hours
    - SLE

Type IV Hypersensitivity
- **T-Cell Delayed type**
- mechanism
  - First contact is asymptomatic and causes differentiation of naive CD4+ T cells to TH1
  - Subsequent contact causes memory response; CD4+ lymphocytes interact with HLA II and antigen
  - IL-2 and cytokines from CD4+ recruit macrophages which cause local inflammation
- **pathology**
  - Localized reddening and induration peaks at 24-72hr
  - Mononuclear cell perivascular cuffing
- **Examples**: contact dermatitis, tuberculin reaction

Type IV Hypersensitivity- mechanisms
- Antigen presented by APC’s to CD4+ cell (via MHC class II)
- T cell releases lymphokines that activate CD8+ cells, NK cells, and fibroblasts; leads to local mononuclear infiltrate
- CD8+ cells also activated by MHC I
- Cell lysis caused by CTL (granules/fas ligand) and NK cells → vesicle formation
- Mild reaction → fibrosis, chronic rxn → granuloma
- Timeframe of response: primary exposure-7-10 days; subsequent exposure- 1-3 days
- Examples: PPD test, poison ivy
Granuloma formation

- **Granuloma**: a focus of epithelioid macrophages and multinucleated giant cells, surrounded by lymphocytes
- **Process (Type IV hypersensitivity):**
  1. Antigen deposition and uptake by macrophages
  2. Release of IL-2 from macrophages; activation of T_h-cells
  3. Release of INF-γ from T_h-cells; activation of macrophages
  4. Inability to clear antigen; cont’d stimulation of macrophages
  5. Formation of multinucleated giant cells
- **Types of multinucleated giant cells:**
  - Foreign body type: nuclei are centrally located and less organized
  - Langhans type: nuclei arranged in arc at periphery of cell (TB type)

HLA, MHC—Autoimmunity

- Autoimmunity is initiated by disease-associated HLA allotypes presenting antigens to autoimmune T cells
- Autoimmunity requires a breach of T-cell tolerance, which implies that the autoimmune response is started by autoreactive T cells being stimulated by specific peptide: MHC complexes.
- More HLA class II associations is expected because they present antigens to CD4 T cells, which are initiators of an immune response.

<table>
<thead>
<tr>
<th>Autoimmune Disease</th>
<th>HLA Allotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>DQ8 and DQ2</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>DQ6</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>DR4</td>
</tr>
<tr>
<td>Myasthenia Gravis, Addison’s Disease, Graves’ Disease</td>
<td>DR3</td>
</tr>
<tr>
<td>Psoriasis vulgaris</td>
<td>Cw6</td>
</tr>
</tbody>
</table>

Infections and Immunodeficiency

<table>
<thead>
<tr>
<th>Lack of Immunoglobulin (IgG)</th>
<th>Bacterial infections Begins at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of T cell function</td>
<td>Viral, fungal infections</td>
</tr>
<tr>
<td>Phagocyte dysfunction</td>
<td>Skin infection, abscesses (catalase positive Staph); klebsiella, E. coli</td>
</tr>
<tr>
<td>Complement dysfunction</td>
<td>C3 or C5-9 Encapsulated organisms (Neisseria, H. influenzae, Strep pneumoniae)</td>
</tr>
<tr>
<td>Severe Combined Immunodeficiency</td>
<td>Early, severe infections of all types</td>
</tr>
</tbody>
</table>

Immunodeficiencies – Both B & T Cell

- **SCID:** Primary lack of both B/T cells- multiple causes
  - 50% caused by adenosine deaminase deficiency
    - Purine toxicity for lymphocytes
  - 50% x-linked mutation of interleukin receptors
    - Common transduction protein for JAK-STAT signaling
    - IL-2, IL-4, IL-7, IL-15, IL-21
    - recurrent infection
    - failure to thrive → death within 1 year
    - Graft-versus-host diease due to blood transfusions

- **Ataxia-Telangiectasia**
  - associated with IgA deficiency; cerebellar ataxia, spider angiomas (telangiectasia), IgM high and IgE low
  - recurrent respiratory infections
  - variable degrees of T cell deficiency
  - lymphoid neoplasms

- **Wiskott-Aldrich:** X-linked disorder which characteristics include thrombocytopenia, eczema, recurrent Infections
  - poor response to polysaccharide antigens → IgM low, IgG NORMAL, IgA/IgE HIGH
  - Associated risk of malignant lymphoma

Immunodeficiencies – Both B & T Cell

- **DiGeorge syndrome (Thymic aplasia):** Selective T-cell deficiency secondary to failure of thymic maturation
  - Failure of third and fourth pharyngeal pouches to develop
  - Thymus and parathyroids fail to develop (none on x-ray)
  - Tetany (hypocalcemia) due to hypoparathyroidism
  - Recurrent viral/fungal infections
  - Congenital defect of heart/great vessels. 22q 11 deletion
    - CATCH 22- Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia and microdeletion of chromosome 22

- **Chronic Mucocutaneous Candidiasis:** T cell dysfunction to Candida albicans causing skin/mucous membrane infections
- **IL-12 receptor deficiency:** disseminated mycobacterial infection due to ↓Th1 response.
### B Cell Deficiencies

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Bruton’s agammaglobulinemia | - X-linked recessive  
- Defect in tyrosine kinase gene  
- Low levels of all classes of immunoglobulin and B cells  
- Recurrent bacterial infections >6mths (maternal IgG protects until then) |
| Hyper-IgM syndrome  | - Defect in CD40 ligand on CD4 T helper cells  
- Inability of isotype switching, high IgM  
- Low IgG, IgA  
- Early severe pyogenic infections, young child (not infant) |
| Common variable immunodeficiency | - Hypogammaglobulinemia w/ B cell hyperplasia  
- Presents in childhood/adolescence  
- Recurrent bacterial infections/GIARDIA/herpes |
| Selective IgA deficiency | - Presents >2y.o.  
- Repeated URI/GI infections |

### Phagocytic Cell Deficiencies

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Leukocyte adhesion deficiency (LAD) | - LAD-1: defect in CD11/CD18 integrins  
- LAD-2: defect in selectin oligosaccharids ligands |
| Chediak-Higashi Syndrome | - AR  
- Neutropenia, defective fusion of lysosomes with phagosomes  
- Recurrent pyogenic infection by Staph/Strep, increased lymphoreticular neoplasms |
| Chronic granulomatous disease | - X-linked  
- Defect in phagocytosis of neutrophils → NADPH oxidase deficiency  
- Susceptible to bacteria (S.aureus), E.coli, Aspergillus  
- Dx: negative nitroblue tetrazolium dye test |

### Complement Deficiencies

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>- Critical for both classical and alternative pathways; associated with infections with pyogenic bacteria</td>
</tr>
</tbody>
</table>
| Deficiency of C1q esterase inhibitor | - Uncontrolled C1esterase activation with generation of vasoactive C2 kinin  
- “hereditary angioedema” |
| Deficiencies of later components (C6-8) | - Neisseria |
| Deficiency of DAF (decay accelerating factor) | - Complement-mediated lysis of RBC’s and paroxysmal nocturnal hemoglobinuria (PNH) |

### Type IV Hypersensitivity - Examples

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin (PPD), histoplasma, coccidioides skin test</td>
<td>- &gt;10mm induration (not erythema) indicates previous exposure to antigen</td>
</tr>
</tbody>
</table>
| Candida skin test | - Like above, but used as a test of cell-mediated immunity  
- Universal candida exposure in human species  
- Failure to respond indicates cell-mediated immunodeficiency |
| Poison ivy | - Lipid-soluble pendecatechol diffuses through cell membranes and binds to intracellular proteins  
- Creates non-self antigens to which no tolerance has developed |
| Contact dermatitis | - After poison ivy, metal allergy (esp. nickel) is second most common |

### Amyloid Structure

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein matrix</td>
<td>- 95% amyloid protein and 5% P component (a normal serum glycoprotein with structural homology to C-reactive protein)</td>
</tr>
</tbody>
</table>
| Amyloid protein | - Characteristic ß-pleated sheets:  
- Arranged into 7.5 to 10nm diameter packed fibrils of indefinite length |
| P component | - >10nm diameter, pentagonal, doughnut-shaped structure with 5 globular sub-units |
| Hyaline, eosinophilic extracellular deposits | - Pressure atrophy of adjacent cells |
| Congo red binds to ß-pleated sheet structure | - Green birefringence regardless of protein subtype |
Primary Amyloidosis

- AL protein type; most common form in USA
  - Overproduction of lambda light chains (Bence-Jones protein)
  - Associated with B-cell dyscrasias, but most amyloidosis does not involve overt malignancy, and vice versa
- Kidney: primarily glomerular deposits
  - Mesangial deposition with widening of basement membrane and obliteration of glomerular space
  - Nephrotic syndrome
- Heart: deposits between muscle fibers
  - Restrictive cardiomyopathy with insidious congestive heart failure
  - Subendocardial deposits can cause conduction abnormalities
- Also GI tract, nerves, skin, tongue

Other Forms of Systemic Amyloidosis

- Senile amyloidosis
  - Transthyretin, a plasma protein that binds thyroid hormone and retinoids
  - Systemic, but cardiac involvement is the dominant pathology
- Hemodialysis
  - Unfiltered β2-microglobulin in synovium, joints, tendon sheaths
  - Carpal tunnel syndrome
- Heredofamilial
  - AA protein in familial Mediterranean fever
  - Transthyretin deposits causing polyneuropathy

Forms of Local Amyloidosis

- Nodular deposits with lymphocytic infiltrate and plasma cells in lung, larynx, skin, bladder, tongue, periorbital region
- Endocrine amyloid
  - Medullary carcinoma of the thyroid (calcitonin)
  - Other polypeptide hormones
  - Islet amyloid polypeptide in type II diabetes
- Alzheimer’s disease
  - Cleavage of amyloid precursor protein leads to β-amyloid deposits in brain

Secondary Amyloidosis

- Also known as reactive systemic amyloidosis associated with chronic inflammation. Chronic tissue destruction leads to increased SAA (serum amyloid-associated protein)
  - Seen in rheumatoid arthritis, TB, osteomyelitis, syphilis, and leprosy
  - There is a deposition of fibrils consisting of amyloid protein which is formed from a precursor, serum amyloid-associated protein (SAA) which is an acute phase reactant
  - Tissues involved include: kidney (nephrotic syndrome), liver, adrenals, pancreas, lymph nodes, and the spleen.

Types of Amyloid Protein

- AL (Amyloid Light Chain) - derived from the immunoglobulin light chains; associated with multiple myeloma
- AA (amyloid associated) - derived from SAA and found in secondary (reactive systemic) amyloidosis
- Aβ (Beta Amyloid) - found in brain lesions of Alzheimer’s disease patients
- ATTR (Transthyretin) - present in senile amyloidosis
- ABeta2m (Beta-2 microglobulin) is a normal component of blood that builds up in patients on long term dialysis.
Transplantation Reactions

• Hyperacute Rejection:
  – Irreversible, occurs within minutes of organ transplant.
  – Pre-formed antibody reacts with vascular endothelium of grafted organ.
    • Antibodies may be against ABO blood groups or anti-HLA antibodies (increased in multiparous women and recipients of multiple blood transfusions).
  – Complement fixation leads to vessel damage -> vessel thrombosis -> ischemia of the graft.

Transplantation Reactions Cont’d

• Acute Rejection
  – Reversible, occurs within days to months.
  – CD4+ cells stimulated by foreign MHC on donor or recipient antigen presenting cells
    • Cellular response leads to interstitial lymphocytic infiltrate of macrophages and CD8+ cells which damage graft tissue
    • Humoral response leads to plasma cell production of anti-HLA antibodies.
  – Immune complexes cause Vasculitis and thrombosis.
  – Vascular damage and cytokines lead to intimal thickening with narrowing of vascular lumen -> graft ischemia.

• Chronic Rejection
  – Occurs within months to years, less well understood.
  – Continued vascular injury to tissue leads to obliterative intimal fibrosis of blood vessels -> ischemia of graft.

Fluid and Hemodynamics

• Non-inflammatory edema – due to
  – ↑d hydrostatic pressure (local venous obstruction, ↑d venous pressure/congestion, ↑d intravascular volume).
  – ↓d plasma oncotic pressure – loss of albumin (nephrotic syndrome, protein-losing gastroenteropathy), ↓d albumin synthesis (cirrhosis, malnutrition, lymphatic obstruction, Na+ retention).
  – Lymphatic blockage.
  – Transudate – low protein, low cells, specific gravity <1.012

• Inflammatory edema – due to ↑d vascular permeability (cytokines, trauma to endothelial cells, angiogenesis)
  – Exudate – high cells, low glucose, specific gravity >1.020.
  – Three-Test Rule (Pleural Fluid)
    • protein >2.9 g/dL
    • cholesterol >45 mg/dL
    • LDH >0.45 times the upper limit of the laboratory’s normal serum LDH

• Hyperemia (active hyperemia) – inflammatory cytokines → arterial/arteriolar dilatation → increased flow into capillary beds; *RED*/flushed
  – Ex: heat dissipation (fever, exercise), blushing, inflammation.

• Congestion (passive hyperemia) – impaired venous drainage → blood accumulation in capillaries; *BLUE-RED*
  – Ex: heart failure
  – Acute – shock, acute inflammation, sudden right CHF
  – Chronic – usually left CHF or mitral stenosis.

• Right CHF – nutmeg liver (centrilobular necrosis)
  – Chronic congestion → necrosis and fibrosis (cardiac cirrhosis).

• Left CHF – causes pulmonary edema; alveolar macrophages phagocytose RBCs → “brown induration” & “heart failure cells”

• Hemorrhage
  – Accumulation in a tissue → hematoma
  – Minute 1-2 mm into skin, mucous membranes, serosa-petechiae (associated with thrombocytopenia)
  – >3mm hemorrhages – purpura associated with petechia, vasculitis
  – >1 to 2 cm subcutaneous hematomas - ecchymoses
  – Large accumulations named by location – ie hemopericardium, hemothorax

• Significance depends on volume and rate of bleeding
  – Rapid (up to 20% loss) – hypovolemic shock
  – Chronic, slow loss – iron deficiency
Virchow’s Triad

- 3 factors that predispose to venous thrombosis
  - Hypercoagulable State: dehydration (EtOH, caffeine), hormones (estrogen), hyperlipidemia, malignancy, inherited clotting disorders, pregnancy, hyper-homocysteinemia
  - Stasis: inactivity, varicose veins, heart failure, hyperviscosity
  - Endothelial Injury: smoking, surgery, trauma

Thrombosis General

- Intravascular mass attached to the vessel wall composed of platelets, coagulation factors, RBCs
- Formation Virchow’s Triad-
  - endothelial cell injury (MOST IMPORTANT)
    - NOTE: does NOT have to be denudation, can be any disruption in the balance of pro- and antithrombotic effect of the endothelium
  - Stasis/turbulence- important in venous thrombi
  - Hypercoagulable state
- Types: arterial, venous (antemortem ONLY)
- Fate: Propagation, embolization, dissolution, organization and recanalization

Thrombosis Morphology

- Arterial Thrombus:
  - Grow retrograde from point of attachment
  - Most common in coronary>cerebral>femoral artery
  - Usually gray/white friable superimposed on atherosclerotic plaque
  - Lines of Zahn- alternating layers of pale platelets and fibrin with darker layers of red cells

- Venous Thrombus:
  - Extend from point of attachment in direction of blood flow
  - Deep veins of lower extremities below the knee
  - Adherent, occlusive dark red- RBC and fibrin
- Post-mortem Clot:
  - Not attached to vessel wall – NOT a true thrombus
  - Upper chicken fat layer (supernatant) & lower currant jelly layer (contains RBCs).

Ischemia

- Ischemia – reduced arterial blood flow
  - Occurs in response to significant drop in blood pressure or occlusion of artery
  - Most common cause of cell injury – coagulative necrosis (except in brain)
- Different from hypoxia- any state of reduced oxygen availability
- Ischemia tends to injure cells faster because it compromises the delivery of glycolytic enzymes and removal of wastes

Coagulation and Hemostasis

- Thrombosis=formation of clots in non-interrupted vasculature
- Intact endothelial cells resist thrombosis by:
  1. Heparin-like molecules activate antithrombin III neutralize thrombin & factor Xa (XII, IX, XI too)
  2. Synthesize prostacyclin (PGI2) & NO inhibit platelet activation and vasodilate
  3. Secrete tPA activates prothrombin
  4. Degrade ADP (ADP is pro-thrombotic)
  5. Synthesize thrombomodulin which binds thrombin to activate Protein C which, with Protein S, cleaves factors Va, Vlla
Platelet Aggregation

- ADP - highly potent mediator of platelet aggregation
- TxA2 - produced by platelets; also causes vasoconstriction
- Thrombin - formed by activation of coagulation cascade; binds to thrombin receptors on platelets
- Gpllb-IIIa complexes - binds activated platelets to fibrinogen (deficiency - Glanzmann thrombasthenia)
- VonWillebrand factor – mediates binding of platelets to collagen (via GPIb; deficiency - Bernard-Soulier syndrome)
- Platelet Factor 3 – cell surface membranes of platelets that allow assembly of coagulation proteins
- Calcium

Coagulation and Hemostasis

- Hemostasis = formation of blood clots at the site of vascular injury
- Damaged blood vessels initiate hemostasis by:
  1. Endothelial cells produce vWF (alpha granules platelets also) → binds Gpllb on platelets to exposed collagen
  2. Tissue factor (aka thromboplastin or factor III) release activates extrinsic path (factor VII)
  3. Platelets synthesize thromboxane A2 → vasoconstriction and platelet aggregation
  4. Fibrinogen links platelets via gpllb-IIIa (1° hemostatic plug)

Coagulation and Hemostasis

- Extrinsic pathway
  - Initiated by tissue factor (thromboplastin)
  - Tissue factor activates factor VII → factor VII activates factor X
  - Prothrombin time (PT), measures VII and factors of common pathway (PT for war (warfarin) at 7am)
- Common Pathway
  - Xa + Va + platelet factor 3 + Ca++ (prothrombin complex, on platelet membrane) → converts prothrombin to thrombin → converts fibrinogen to fibrin → stabilized by XIII (XIII activated by thrombin)

Coagulation and Hemostasis

- Intrinsic Pathway
  - Factor XII (Hageman) activated by exposed collagen or HMWK
  - XIIa activates 1) factor XI 2) plasminogen 3) kininogen system (bradykinin and kallikrein)
  - Factor XIa activates factor IXa + factor VIIIa + PF3 + Ca++ complex to activate factor X of the common pathway
  - Partial Thromboplastin Time (PTT) measures, VIII, IX, XI, XII, and factors of the common pathway (for monitoring heparin)
  - Hageman Factor XIIa links the fibrinolytic system, coagulation system, complement system, and kinin system.

Coagulation and Hemostasis

- Fibrinolysis (thrombus dissolution)
  - Plasminogen → plasmin by tPA (alteplase, retelase) or Xllia
  - Plasmin cleaves fibrin (D-dimers) and fibrinogen (FDPs)
  - Plasmin also degrades factors V and VII
- Anticoagulants
  - Antithrombin III: inhibits thrombin & factors IXa, Xa, Xlla, Xllia, heparin modulates activity of ATIII
  - Protein C & S: Vit K dependent; inactivate Va, Vlla.

Coagulopathy: Vascular damage

- Petechia, epistaxis, prolonged bleed time, normal PT/PTT
- Scurvy: vit C def causing weak capillaries and venules
  - low hydroxylation K + P = low tropocollagen crosslinks
  - gingival/subQ bleed, poor wound healing, ecchymosis
- Henoch-Scholein purpura: hypersensitivity vasculitis w/ immune damage endothelium, fever, arthralgia, renal/GI
  - hemorrhagic urticaria (palpable purpura)
- Waldenstrom's Macroglobinemia: hyperviscosity
- CT disorders: abnormal collagen/elastin-vascular bleeding
- RMSF/Meningioccocus: necrosis/rupture of small vessels
### Coagulopathy: thrombocytopenia
- **Epistaxis, petechia, GI/intracranial bleed, prolonged bleed time**
- **ITP**: IgG antibodies against GpIIb:IIa
  - kids: acute, self-limited after viral URI
  - adults: chronic idiopathic, associated with HIV and SLE
  - no lymphadenopathy or splenomegaly
- **TTP**: acquired or genetic deficiency in VWF-cleaving metalloproteinase
  - pentad: microangiopathic hemolytic anemia (schistocytes), fever, thrombocytopenia, renal insufficiency, neurologic abnormalities

### Blood Groups
- Determined by glycoproteins attached to RBC surface
- **Blood Group O**: no antigens on surface, anti-A and anti-B IgM, most common blood group.
- **Blood Group A**: A antigen, anti-B IgM, increased gastric carcinoma.
- **Blood Group B**: B antigen, anti-A IgM.
- **Blood Group AB**: both A and B antigens, no antibodies, least frequent blood group
- **Rh group**: 5 different antigens, either Rh + or Rh -

### Blood Type Abs/Bombay Type
- Transferase adds carbohydrate moieties onto H substance
  - Bombay type has NO H substance → have anti-A, anti-B Abs
  - A - N-acetylgalactosamine added → have anti-A Abs
  - B - D-galactose added → have anti-A Abs
  - O – most common, no transferase → have anti-A, anti-B Abs
- **ABO Abs are naturally occurring, usually IgM**
  - Activate complement → cause intravascular hemolysis
- **Rh Abs** – not naturally occurring, mostly IgG
  - Cross placenta → cause extravascular hemolysis
- **ABO and Rh status determined by indirect Coombs**

### ABO Incompatibility in Transfusions
- Antibodies to A and/or B antigens bind the transfused erythrocytes leading to complement fixation and removal from the circulation by the spleen
- Pathogenesis is identical to that seen in type II hypersensitivity reactions
- Symptoms include hemolytic anemia, chills, shock, renal failure and possible death

### ABO Incompatibility in Transplant
- **Hyperacute graft rejection**
- Antibodies react with antigens on the vascular endothelial cells of the graft and initiate complement and clotting cascades
- Vessels become blocked with clots leading to death of the graft
- Gross pathology: graft is engorged and purple colored from hemorrhaged deoxygenated blood

### Immune Hydrops
- Results from immunization of the mother by blood group antigens on fetal red cells usually during the 3rd trimester
- 1st exposure leads to production of IgM which cannot pass through the placenta (immune hydrops is not seen in 1st pregnancies)
- A second exposure produces IgG antibodies to the fetal RBC antigen and crosses the placenta
- Complement fixation is induced and coated RBCs are cleared by the spleen (extravascular)
Immune Hydrops, Cont’d

- Hemolysis leads to anemia and/or jaundice
- If hemolysis is mild, extramedullary hematopoiesis will prevent anemia
- If severe, anemia causes hypoxic injury to heart and liver - albumin and other protein synthesis is impaired; along with heart injury leads to edema
- Increased unconjugated bilirubin from hemolysis binds lipids creating a poorly developed BBB and kernicterus

Rh Factor Immune Hydrops

- Rh system incompatibility is the most common cause of immune hydrops
- D antigen is the major cause
- Rh incompatibility hydrops is prevented by maternal injection of Rhlg (Rhogam) at 28 weeks and within 72 hours of the delivery of the 1st child and all subsequent children in a woman that is Rh- and does not yet have anti-D antibodies

ABO Immune Hydrops

- ABO incompatibility seen in 20-25% of pregnancies, only 1 in 10 of these has hemolysis and 1 in 200 requires treatment
- Most ab is IgM; neonatal cells express A & B antigens weakly; other cells also have blood group antigens and sequester the antibody
- Seen most often in A or B infants born to type O mothers who make some IgG to A & B antigens

Type and Screen/Crossmatch

- Type and screen- determines recipient blood type and presence of serum anti-RBC antibodies; screen for ab to RBCs; no precipitation of RBCs = no antibodies present, no blood actually set aside
- Type and Cross- units intended for patient are incubated with patient serum and an Indirect Coombs test is preformed; negative Indirect Coombs indicates the blood is ABO compatible, not reusable after cross.

Shock

- SHOCK = circulatory collapse → impaired tissue perfusion → systemic hypoxia
- Brain is the first organ affected
- Medical emergency! Need to reverse cause of hypoxia
- Some types require aggressive volume replacement
- Stages → ends w/ irreversible end organ damage
  - Nonprogressive- compensatory mechanisms
    - ↑HR, ↑TPR; perfusion maintenance of vital organs
    - Progressive- onset of tissue hyperperfusion & circ/metabolic imbalance
    - Ex. metabolic acidosis due to lactic acidemia
  - Compensatory mechanisms no longer adequate
  - Irreversible – damage too severe – survival impossible
- Signs: acute tubular necrosis, GI mucosal hemorrhages, pulmonary edema, fatty change

Shock Types - Hypovolemic

- Circulatory collapse b/c fluid loss
  - Normal = 9 units or 4-5 liters
  - Loss of 10-15% without clinical sequelae
  - Loss of 15-30% - tachycardia
  - Loss of 30-40% - worsening of mental status
  - >40% - limit of compensation and risk of death
  - Hemorrhage, severe trauma, fluid loss via skin (ex. 3rd degree burns), diarrhea, vomiting
  - Pulmonary capillary wedge pressure (PCWP) b/c LV EDV
  - Mixed venous oxygen content (tissues have time to extract more oxygen than nL)
  - Cold skin b/c of peripheral vasoconstriction (sympathetic)
  - If due to blood loss, IV crystalloid solutions will reveal ▽ RBC
  - Therapy - replace volume w/ whole blood
Shock Types – Cardiogenic
- Circulatory collapse b/c of pump failure of the LV
- MCC= acute MI
- other causes: PE, arrhythmias, cardiac tamponade, pulmonary saddle embolus (↓↓ blood return to LA)
- ↑PCWP (b/c fluid back-up into pulmonary v.v.)
- normovolemic
- other signs are similar to hypovolemic shock
- *NEUROGENIC-loss of ANS (brain stem or cord damage)
- ↓ HR, ↓TPR (b/c loss of tonic sympathetic stim.)
- warm, dry skin, venous pooling
- normovolemic

Shock Types - Neurogenic
- Due to loss of vascular tone
  - Tone loss secondary to loss of ANS (brain stem or cord damage)
  - ↓ HR, ↓TPR (b/c of loss of tonic sympathetic stim.)
  - warm, dry skin (can’t vasoconstrict), venous pooling
  - normovolemic

Septic Shock/Sepsis
- **Sepsis** = blood infection + systemic inflammatory response
- Most associated w/gram negative infection (bug expressing LPS or LOS)
  - Causes gram-negative endotoxemia
  - Same result can happened from injecting LPS alone
- Septic shock results from sepsis
- Septic shock also seen w/gram positive and other infections

Septic Shock/Sepsis
- Endotoxins (LPS, LOS - lipid part of cell wall) cause release of IL-1, IL-6, TNF by monocytes
  - Activated complement and kinin systems → direct toxic injury to cell
  - Endothelial cell damage releases nitric oxide – vasodilates & can activate coagulation cascade (+/- DIC)
  - CO may initially increase due to vasodilation
- Systemic ↑ in vascular permeability → hypovolemia
- Warm, pink skin, organ hypoxia
- organ dysfunction is due both to hypoxia and systemic cytokine release

DIC
- Activation of DIC
- Pathogenesis
- Clinical associations
  - Sepsis, *Neisseria meningitidis*
- Clinical measures – D-dimer; fibrinolytic peptides
- Pathologic findings

Acid-Base
Henderson-Hasselbach
  \[ \text{pH} = 6.1 + \log(\text{HCO}_3^-)/\text{pCO}_2 \times 0.03 \]
- General considerations
  - pH rises with ↑HCO$_3^-$ or ↓pCO$_2$
  - pH falls with dec HCO$_3^-$ or inc pCO$_2$
  - dec pH w/inc CO$_2$ = respiratory acidosis (HCO$_3^-$ >30)**
  - dec pH w/dec CO$_2$ = metabolic acidosis (HCO$_3^-$ <22)
  - inc pH w/dec CO$_2$ = respiratory alkalosis (HCO$_3^-$ <18)**
  - inc pH w/inc CO$_3^-$ = metabolic alkalosis (HCO$_3^-$ > 28)
- ** if compensated metabolically
Acid-Base

Clinical considerations
- CO₂ changes reflect respiratory function
- HCO₃ changes reflect renal/metabolic function
- Compensatory mechanisms: renal function altered to compensate for respiratory disease while respiratory function is altered to compensate for metabolic or renal disease
- The resulting attempt to compensate is never complete (pH never gets back to 7.4).

Total CO₂
- Total CO₂(mEq/L) = HCO₃ + pCO₂*0.03

Serum potassium is often increased with acidosis and decreased in alkalosis

Anion Gap may increase with metabolic acidosis
- AG= Na-(Cl + HCO₃) THINK MULEPAK

Acidosis can be treated with bicarb to neutralize acid or hyperventilation to breathe off excess CO₂

Alkalosis can be treated by hypoventilation, retention of H⁺, or excretion of HCO₃⁻

Control of Growth – Tissue Proliferation

Labile tissues – Continuously dividing tissues (i.e. skin, surface epithelia, mucosa of glands and GI)
Quiescent tissues – Normally have a low level of replication but can regenerate if needed (i.e. liver, kidneys, pancreas, fibroblasts and smooth muscle)
Permanent tissues - Terminally differentiated cells with little to no regenerative capability (i.e. neurons, skeletal muscle, and cardiac muscle)

Control of Growth – Growth Factors

EGF & TGFα – Similar factors that stimulate keratinocyte migration and granulation tissue formation
VEGF – Induces angiogenesis and increases vascular permeability is important in tumor growth
PDGF – Causes migration and proliferation of fibroblasts and smooth muscle and is important in wound healing
FGF – Angiogenesis, wound repair, skeletal muscle development and lung maturation, and hematopoiesis.
TGFβ – Growth inhibitor for epithelial cells and leukocytes, stimulates fibroblasts and smooth muscle cells, strong anti-inflammatory effect, and potent promoter or fibrosis

Control of Growth – Control Points

Cyclin-dependent kinase (CDK) – Proteins that serve as checkpoints between cell cycle phases by phosphorylating proteins (ie: RB) vital to cycle transition
Cyclin – Proteins that are synthesized during specific phases and then rapidly decline after their function is complete.
- Function→ phosphorylate inactive CDKs rendering them active
CDK inhibitors – Prevent the movement from one cell cycle point to the next by inhibiting CDK.
- Cip/Kip and INK4/ARF are examples
- Serve as tumor suppressors and frequently altered in tumors

Resting cells are in G0 and are recruited into G1
Orderly progression through phases is regulated by cyclins and CDKs:
- CyclinD/CDK4→ phosphorylates RB allowing passage through the G1 restriction point.
- CyclinE/CDK2→ permits DNA replication
- CyclinA/CDK2→ regulates mitotic prophase
- CyclinB/CDK1→ regulates nuclear division
Cell cycle has 2 check-points
- Between G1/S and G2/M
- If DNA damage present- DNA duplication is arrested
- If DNA damage is repairable- repaired, if not undergoes apoptosis

Control of Growth
### Neoplasia - Definitions

- **Hyperplasia** – physiologic or pathologic increase in number of cells in a normal arrangement (reversible)
- **Metaplasia** – replacement of one fully differentiated cell type by another fully differentiated cell type (reversible)
- **Dysplasia** – pre-neoplastic pleomorphic cells (change in cell size, shape and organization (reversible)
- **Anaplasia** – lack of differentiation marked by: pleomorphism, hyperchromatism, mitosis
- **Neoplasia** – uncontrolled clonal cell proliferation
- **Grade** – degree of cellular differentiation (I to IV)
- **Stage** – degree of spread from primary lesion (TNM)

### Neoplasia – Definitions cont.

- **Adenoma** – benign neoplasm of parenchyma derived from glands or forming glandular patterns
  - Sebaceous gland adenoma
  - Ovarian cystadenoma
- **Papilloma** – benign neoplasms that form microscopic papilla
- **Adenocarcinoma** – malignant neoplasm of parenchyma derived from glands or forming glandular patterns
  - Sebaceous gland adenocarcinoma
  - Ovarian cystadenocarcinoma
- **Leukemia** – malignant lymphoid neoplasm with widespread involvement of the bone marrow and tumor cells often in peripheral blood
- **Lymphoma** – malignant lymphoid neoplasm that arise in discrete tissue masses outside of the bone marrow

### Neoplasia - Definitions

- **Hemangioma** – benign accumulation of blood vessels
- **Hemangiosarcoma** – malignant blood vessel tumor
- **Leiomyoma** – benign smooth muscle tumor
- **Leiomyosarcoma** – malignant smooth muscle tumor
- **Rhabdomyoma** – benign skeletal muscle tumor
- **Rhabdomyosarcoma** – malignant skeletal muscle tumor
- **Osteoma** – benign bone tumor
- **Osteosarcoma** – malignant bone tumor
- **Lipoma** – benign fat tumor
- **Liposarcoma** – malignant fat tumor
- **Carcinoma in situ** – no surrounding tissue invasion

### Neoplasia – Definitions cont.

- **Mature teratoma** – benign, from the 3 germ cell layers
- **Immature teratoma** – malignant, same derivation
- **Carcinoma** – malignant tumor of epithelial origin
- **Sarcoma** – malignant tumor of mesenchymal origin
- **Invasion** – spread to adjacent tissues
- **Metastasis** – spread to nonadjacent tissues
- **Desmoplasia** – non-neoplastic, tumor-induced fibrous tissue
- **Choristoma** – normal tissue in another organ (benign)
- **Hamartoma** – benign disorganized overgrowth in appropriate organ
- **Proto-oncogene** – regulate cell growth & differentiation

### Oncogenes

- **genes** from the normal genome which are now altered in structure or expressed in abnormal amounts.
- **Dominant Oncogenes** – are elements that promote growth only need expression of a single allele to cause unregulated proliferation (RAS, growth factors, growth factor receptors)
- **Recessive Oncogenes** – are elements that inhibit growth require loss of both alleles to eliminate the inhibitory signal (Tumor suppressor genes, DNA repair genes).
### General Tumor Oncogenes
- **p53** – loss of both alleles is most common genetic mutation in human cancer; loss of cell cycle arrest; loss of apoptotic mechanisms (not necrosis)
- **BCL2** – inhibitor of apoptosis; over-expression or mutation results in arrest of apoptosis in neoplasms (Follicular lymphoma)
- **RAS** – most common oncogene in development of human cancers; trapped in activated GTP-bound state
- **MYC** – transcriptional activation associated with gene amplification; activated in Burkitt’s lymphoma

### Specific Tumor Oncogenes
- **BCR-ABL** fusion product – increased tyrosine kinase activity (CML, Philadelphia chromosome)
- **HNPCC** – hereditary nonpolyposis colon carcinoma – patients inherit 1 defective copy of mismatch repair genes; results in microsatellite instability
- **APC** – tumor suppressor gene inactivated in colon cancer; APC-β-catenin signalling of gene transcription; WNT signaling pathway

### Specific Tumor Oncogenes
- **ERBB2** (HER2) – non-familial breast carcinomas; up to 1/3; amplification of growth factor receptor; poor prognosis
- **NF1** – neurofibromatosis type 1 – traps RAS in active state
- **RB** – retinoblastoma – 2 hit hypothesis
  - In familial forms, 1 mutated allele is inherited
  - Controls transition from G1 to S; loss of cell cycle “checkpoint”
- **Neuroblastoma** – MYC amplification (poor prognostic sign)

### Specific Translocations
- t(9;22) – Philadelphia chromosome – CML – c-ABL on chromosome 9 to fuse with BCR on chromosome 22
- t(11;14) – Mantle zone lymphoma – BCL1
- t(14;18) – Follicular lymphoma - BCL2 gene with immunoglobulin heavy chain gene
- t(8;14) – Burkitt’s lymphoma – amplification of MYC to cause transcriptional activation

### Viral Oncogenes
- **Human papilloma virus**
  - HPVs 16, 18, 31 encode proteins that bind p53 with high affinity
  - Inactivate tumor suppressor genes p53 and RB
    - E7 binds to RB
    - E6 inactivates p53
- **Hepatocellular carcinoma**
  - Hepatitis B, Hepatitis C; No transforming proteins
  - Regenerating hepatocytes undergo mutations such as loss of p53
  - Virus-induced injury followed by extensive regeneration

### Viral Oncogenes
- **HTLV**
  - T cell lymphoma
  - Monoclonal population with T cell markers such as CD4
  - Develops in 1% of those infected with the virus
- **EBV**
  - Burkitt’s lymphoma
  - Hodgkin’s disease
  - Nasopharyngeal carcinoma
RAS

- single most common abnormality of dominant oncogenes in human tumors
- 30% of all human tumors contain mutated versions of ras
- (Colon, Pancreas and Thyroid highest rates)
- Mutated ras proteins can be activated by GTP binding but can not be inactivated by GTPase activity leading to constitutive activity
- An example of a signal transduction protein → works through MAP kinase pathway

RB (Retinoblastoma Protein)

- acts as brake to inhibit cells from going from G0/G1 to S phase; Phosphorylation of RB causes dissociation of RB and permits replication
- Recessive Oncogene
- Retinoblastoma a hereditary malignant tumor of retina (40% familial)
- “two-hit” hypothesis of Knudson: One mutated copy of gene is inherited from a parent and the other normal gene undergoes somatic mutation
- Also associated with genesis of osteosarcoma

p53

- single most common target for genetic alterations in human cancer
- Tumors with normal p53 are more likely to be sensitive to chemotherapy and radiation mediated by apoptosis of cells damaged by the chemotherapeutic agent
- Li-Fraumeni syndrome is the familial form similar “two hit” hypothesis
- P53 causes cell cycle arrest of genetically damaged cells mediated through CDK inhibitor p21; If DNA is unable to be repaired then cell undergoes apoptosis mediated through BAX.

DNA Repair Genes

- Absence of repair mechanisms are associated with genetic instability
- Xeroderma pigmentosum Autosomal Recessive condition characterized by defect in nucleotide excision repair gene therefore cannot repair UV induced pyrimidine dimers ; Increased incidence of skin cancers.
- Hereditary non-polyposis cancer syndrome - Defective mismatch repair resulting in microsatellite instability; Familial right-sided colorectal cancers
- BRCA1, BRCA2-associated with Breast and ovarian cancer

Carcinogenesis

- Basics
  - Carcinogenesis involves both genetic damage and induction of proliferation
  - Oncogene: activated by mutation, promotes growth, only one mutation required
  - Tumor-suppressor gene: knocked-out by mutation, growth inhibitors (or DNA repair), both alleles must be mutated
  - Angiogenesis or migration must occur for the tumor to grow to a significant size

Carcinogenesis

- “Initiation”:
  - nonlethal DNA damage that affects oncogenes and tumor-suppressor genes; occurs before promotion
  - examples: UV light, HPV type 16,18 integration
- “Promotion”:
  - may be reversible, promotes proliferation of the damaged cell
  - examples: hormones, inflammation
- “Complete carcinogen” does both (cigarette smoke)
  - inhaled chemicals mutate the DNA
  - smoke causes irritation → inflammation
Carcinogenesis

- Tumor suppressor gene examples
  - RB: inhibits EF2 transcription (prevents G1 entry)
    - Activated by CDK
  - p53: G1/S checkpoint, activates a CDK inhibitor to prevent RB phosphorylation: growth prevention and apoptosis of damaged cells
  - Absent in Li-Fraumeni Syndrome
  - NF-1: Ras suppressor (Neurofibromatosis Type I)
  - BRCA-1 (Breast & ovarian) & 2 (breast)
    - Involved in DNA double strand break repair
    - 2-hit hypothesis: Mutations in tumor-suppressor genes show dominant inheritance. By inheriting a mutated allele, only one mutation is needed to cause cancer.

DNA damage:
- Pyrimidine dimers (radiation, UV)
- Chromosomal breaks (radiation)
- Translocations (radiation)
- Gene amplification (n-myc, ERB B2)
- Viral gene insertion
  - HPV: E6 inactivates p53, E7 inactivates Rb
  - HBV: expression of HBx increases protein kinase C
  - Also EBV, HHV-8, HTLV-1
- Epigenetics: alteration of regulators/promoters

Environmental Carcinogens

- Vinyl chloride – liver angiosarcoma
- Naphthalene – urinary tract cancers
- Benzene – leukemias
- Asbestos – lung cancer (smokers), mesothelioma
- Radiation
  - Thyroid cancer, Bone cancer, Leukemias
- Aflatoxin
  - Aspergillus flavus, peanuts
  - Hepatocellular carcinoma
- Arsenic – skin cancer
- Nickel – respiratory tract cancers
- Cadmium – prostate cancer

Growth and Spread of Tumors

- Telomerase activation: allows cells to divide indefinitely
- Angiogenesis: requires VEGF or TGF-a or b secretion
  - Required for growth/metastasis of tumor – cannot enlarge beyond 1-2 mm due to limited diffusion of O2, nutrients
  - Clinically correlated with: poorer prognosis, tumor growth, metastasis
- Spread
  - Sarcomas – hematogenous spread
  - Carcinomas – lymphatics first, then hematogenous
    - Exceptions: hepato-cellular and renal cell carcinoma are hematogenous
    - Seeding: peritoneal cavity, plural cavity, subarachnoid space

Paraneoplastic Syndromes

- Symptoms that cannot readily be explained by the local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue from which the tumor arose.
- 10% of patients with malignant disease—may be earliest manifestation, may represent significant clinical problems

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Major Cancers</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing Syndrome</td>
<td>Small Cell Carcinoma of the Lung</td>
<td>ACTH or ACTH-like substances</td>
</tr>
<tr>
<td>SIADH</td>
<td>Small Cell Carcinoma of the Lung</td>
<td>ADH or Atrial Natriuretic Hormones</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>Squamous Cell Carcinoma of the Lung</td>
<td>Parathyroid hormone-related protein (PTH/HRP), TGF-β, TNF, IL-1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hydatidiform moles, Choriocarcinoma, Some Lung Neoplasms</td>
<td>TSH or TSH-like substances</td>
</tr>
</tbody>
</table>

Growth and Spread of Tumors

- Invasion & Metastasis
  - Discohesiveness from clonal population: loss of homotypic adhesion proteins [cadherins/catenins]
  - Access to vasculature: leaky angiogenic vessels; Type IV collagenase degradation of basement membranes
  - Binding and growth at distant site: adhesion to epithelium with laminin and fibronectin (CXCR4 and CCR7 receptors on tumor emboli) → egress through basement membrane
  - Mature cartilage and elastic tissue in arteries are resistant to invasion by malignant cells
Paraneoplastic Syndromes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Insulin or Insulin-like substances</td>
</tr>
<tr>
<td>Carcinoid Syndrome</td>
<td>Bronchial Adenoma, Carcinoid, Pancreatic Carcinoma, Gastric Carcinoma</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Renal Carcinoma, Cerebellar Hemangioma, Hepatocellular Carcinoma</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>Bronchogenic Carcinoma</td>
</tr>
<tr>
<td>Lambert Eaton</td>
<td>Thymoma, Small Cell Lung Cancer</td>
</tr>
<tr>
<td>Gout, Urate Nephropathy</td>
<td>Leukemia, Lymphoma, Increased uric acid due to increased cell turnover</td>
</tr>
</tbody>
</table>

Cancer—Highest Incidence

- Female:
  - #1 Breast
  - #2 Lung
  - #3 Colon
- Male:
  - #1 Prostate
  - #2 Lung
  - #3 Colon

Cancer—Highest Mortality

- Female:
  - #1 Lung
  - #2 Breast
  - #3 Colon
- Male:
  - #1 Lung
  - #2 Colon
  - #3 Prostate

Cancer – Take Home Points

- Lifetime probability of developing cancer is greater in MEN
- Men = 1 in 2
- Female = 1 in 3
- Women have a greater chance of getting cancer before age 60.
- Cancer = #2 cause of death in U.S. (#1 = heart disease)
- Cancer rates second to accidents as the leading cause of death in children
- African Americans have highest cancer rates of any race

Age and Cancer

- Incidence of most cancers increases with age
- **Exceptions:** with peak ages (years)
  - Testicular Cancer = 25-29
  - Cervical Cancer = 35-39
  - Thyroid = 30-35
  - Acute Lymphocytic Leukemia = biphasic (children and elderly)
- Incidence increases, but tumors grow more slowly and less aggressively with age.
### Cancer - Hereditary

**Familial Cancers:**
- Retinoblastoma (RB) = Autosomal dominant, loss of RB tumor suppressor gene on chromosome 13
- Xeroderma Pigmentosum = decrease in DNA repair
  - Increase in skin CA, malignant melanoma w/ sun
- Von Hippel-Lindau (VHL) disease – bilateral renal cell carcinomas; VHL tumor suppressor gene on chrom 3
- Neurofibromatosis: Aut Dom. NF2 gene (GTPase) (bilateral schwannomas - type 2)
- Li-Fraumeni syndrome – Auto Dom. loss of p53 tumor suppressor gene
- Multiple Endocrine Neoplasms (MEN), Autosomal dominant inheritance of RET oncogene

### Cancer – Hereditary cont’d

- Breast cancer (BRCA1 and BRCA2 genes)
- Colon cancer (APC gene in familial polyposis, HNPCC gene in hereditary nonpolyposis colorectal cancer)

### Predisposing Conditions for Cancer

**Hormonal:**
- Unopposed ESTROGEN Æ inc. breast and endometrial ca.

**Infectious associations with CANCER:**
- Hep B and Hep. C Æ hepatocellular carcinoma
- HPV Æ squamous cell carcinoma of cervix
- EBV Æ African Burkita’s lymphoma, Hodgkin’s lymphoma
- Schistosome hematobium Æ Sq. cell carcinoma of bladder
- HIV – CNS lymphoma
- Helicobacter Pylori: MALT Lymphoma

**Non-infectious** Chronic inflammation: 
- Barrett’s Esophagus -> adenocarcinoma (metaplasia from squamous to glandular)
- Lung Cancer -> squamous cell carcinoma (squamous metaplasia due to chronic smoke damage)

### Diagnostic Characteristics

- Differentiation of hyperplasia from adenoma
  - Tumors are monoclonal: more important than % dividing or aneuploidy
  - Reactive proliferation is not monoclonal
  - Most important cellular techniques for determining neoplasm
    - Southern blot for T- or B-cell receptor gene arrangements
    - Determine clonality by pattern of X chromosome inactivation
    - DNA content doesn’t reflect expression of genes
- Flow cytometry helps to determine ploidy, expression of surface antigens
  - CD4 on flow cytometry = T cell lymphoma
  - Monoclonal cells give intense signal on flow cytometry
  - HTLV is associated with T-cell lymphomas
- Frozen section – tumor margins
Pathology Review Flash Cards for Revision
Infectious Disease, Rheumatology
Spring 2009

Staph and Strep - General
• Gram+ cocci (staph = clusters; strep = chains)
• Pyogenic → abscess formation
• Suppurative response due to neutrophils → leads to liquefactive necrosis
  – Neutrophils also cause bystander tissue damage
  – Spread along tissue planes
• Opsonization by C3b and phagocytosis important for control of infection, antibodies help neutralize toxins
• Diseases with decreased neutrophil function (diabetes, chronic granulomatous) → increased pyogenic infection

Staphylococci
• Normal flora – common cause of skin abscesses, wound infections
  – Major cause of infection in burns, surgical wounds, nosocomial infections
• Virulence factors for *S. aureus*, *S. epidermidis*, *S. saprophyticus*
  – All Catalase Pos; Only *S. aureus* is coagulase pos.
  – Protein A—binds Fc receptor; protects from opsonization
  – Coagulase—fibrin clot protects from phagocytosis
  – Penicillinase—inactivates penicillin
  – Hyaluronidase—spreading factor; destroys connective tissue
  – Exfoliatin—scalded skin syndrome
  – Enterotoxins—heat stable, food poisoning (milk, meat, mayo)
  – Toxic Shock Syndrome Toxin (TSST-1)—superantigen; binds MHC II and T-cell receptor → polyclonal activation

Streptococci - General
• Suppurative, spreading infections
  – Skin – cellulitis, impetigo, erysipelas, GABHS
  – Upper respiratory – strep throat
• Post-strep hypersensitivity
  – Rheumatic fever (acute/chronic), immune complex glomerulonephritis, erythema nodosum (vasculitis)
• Subtypes
  – Group A – GABHS (S. pyogenes), pharyngitis, post-strep nns
  – Group B – perinatal sepsis, UTIs, pneumonia, meningitis
  – Group D – anaerobic (S. faecalis)/enterococcus
  – Viridans – α-hemolytic, subacute bacterial endocarditis
  – *Strep pneumoniae* – encapsulated, IgA protease → causes meningitis, otitis media in children, pneumonia, and sinusitis

Streptococcus
• Virulence Factors
  – Cell wall polysaccharides/M-protein— inhibits complement/phagocytosis
  – Enzymes: streptokinase (breaks up fibrin), streptolysin O,S (destroys RBCs and WBCs)
  – Erythrogenic toxin – characteristic fever, rash, pain
• Types of infections
  – GABHS – acute pharyngitis (punctate abscesses)
  – Scarlet fever – prolonged Group A pharyngitis, red rash on trunk, strawberry tongue, desquamation of skin
  – Post-strep sequelae – glomerulonephritis (sx of acute renal failure), rheumatic fever
  – Skin – impetigo, pyoderma (superficial layers), erysipelas (middle-aged, warm climate, no suppuration)
### N. meningitidis (Meningococcus)
- Gram-negative diplococcus
- Complex nutritional requirements, especially iron
- Colonizes mucosal surfaces in nasopharynx, can invade and cause purulent meningitis and bacteremia
  - Commonly causes cluster epidemics
- **Virulence factors:** antiphagocytic capsule with LPS, secretion of IgA protease
  - Can lead to DIC, vascular collapse (most common cause of death)
  - Petechial rash indicates systemic dissemination
  - IgA protease facilitates survival on mucosal surfaces
- Short incubation period (<1 wk), can be fatal if not treated quickly

### Haemophilus influenzae
- Gram-negative pleomorphic bacteria
- Upper respiratory, sinus, otitis, pneumonia, meningitis
- Unencapsulated forms cause respiratory infections, colonizes respiratory tract; capsulated forms cause invasive disease
  - Capsule type B (HIB) most common invasive form
  - Causes meningitis in young (1-6 years), epiglottitis (can compromise airway)
  - Has endotoxin characteristics, can cause DIC
- Window of susceptibility – 3 months to 6 years
- Vaccine now available, has reduced incidence of HIB diseases in children
  - Capsular polysaccharides conjugated to protein to boost effectiveness in infants

### Bordetella pertussis
- Gram-negative cocccobacillus, causative agent of whooping cough
- Colonization via **filamentous hemagglutinin adhesin** to carbohydrates on respiratory epithelium and CR3 (Mac-1) on macrophages
- Pertussis toxin (exotoxin) homologous to Cholera and E.coli heat-labile toxin, ADP-ribosylates **Gi protein** allowing unregulated activity of adenylate cyclase to increase cAMP, this paralyzes cilia and promotes lymphocytosis by inhibiting chemokine receptors
- Laryngotracheobronchitis that spares alveoli
- Striking lymphocytosis (**up to 90%**) and enlarged peribronchial lymph nodes

### Corynebacterium diphtheriae
- Gram-positive club, metachromatic granules, grows on tellurite agar
- Phage-encoded A-B toxin **ADP ribosylates elongation factor-2 (EF-2)** inhibiting protein synthesis
- Attachment to upper airway, release of exotoxin causes epithelial necrosis with fibrinosuppurative exudate that coagulates to form **grey superficial membrane**
- Intense neutrophilic infiltrate, neovascularization, interstitial edema of tissue
- **Bacterial invasion remains local**, lymphadenopathy + splenomegaly due to hemotogenous spread of exotoxin
- Toxin also causes **fatty myocardial change and necrosis, polyneuritis** with myelin degeneration

### Nosocomial Infections
- E. coli and Staph Aureus are major players but Klebsiella and Pseudomonas are primarily nosocomial
- **Klebsiella Pneumonia** (gram neg rod)
  - **Aspiration Pneumonia** in hospitalized patients, alcoholics, diabetics may cause **Necrotizing Abscesses**.
  - Urinary Tract Infections seen secondary to obstruction.
  - Septicemia and Meningitis due to its thick mucoid capsule (inhibits phagocytosis).
- **Pseudomonas** (gram neg rod, oxidase +)
  - Ubiquitous in hospital setting, esp in water sources - Respirators!
  - Causes nosocomial pneumonia, urinary tract infection, and wound infection. **Vasculitis** “Blue haze” -> thrombosis & hemorrhage
  - High rate of mortality in **cystic fibrosis, burn**, and **neutropenic** patients
  - Sepsis manifests as **Ecthema Gangrenosum**: DIC due to endotoxin
  - Virulence factors include leukocidin, phospholipase, and **Exotoxin A**
### Food Poisoning/Enteritis

<table>
<thead>
<tr>
<th><strong>• Common Causes:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>– Vibrio parahaemolyticus-contaminated seafood</td>
</tr>
<tr>
<td>– Bacillus cereus – reheated rice</td>
</tr>
<tr>
<td>– Staph. aureus – meats, mayonnaise, custard</td>
</tr>
<tr>
<td>– Clostridium perfringens – reheated meat dishes</td>
</tr>
<tr>
<td>– C. botulinum – improperly canned foods</td>
</tr>
<tr>
<td>– E. coli 0157:H7 – undercooked meat</td>
</tr>
<tr>
<td>– Salmonella – poultry, meat, and eggs</td>
</tr>
<tr>
<td>– S. aureus and B. cereus have the fastest onset</td>
</tr>
</tbody>
</table>

### Food Poisoning/Enteritis - Salmonella

<table>
<thead>
<tr>
<th><strong>• General Characteristics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>– Gram negative rod, flagellate</td>
</tr>
<tr>
<td>– non lactose fermenting, produces H₂S</td>
</tr>
<tr>
<td><strong>• Transmission</strong></td>
</tr>
<tr>
<td>– urine/feces, turtles, undercooked chicken, eggs, meat</td>
</tr>
<tr>
<td><strong>• Pathogenesis</strong></td>
</tr>
<tr>
<td>– invades mucosal cells and cause mucosal ulceration</td>
</tr>
<tr>
<td>– do NOT produce enterotoxins</td>
</tr>
<tr>
<td>– multiply within neutrophils and macrophages</td>
</tr>
<tr>
<td><strong>• Forms</strong></td>
</tr>
<tr>
<td>– Enteric fever – fever, bacteremia, assoc. w/ sickle cell, schistosomiasis</td>
</tr>
<tr>
<td>– Food poisoning – V/D, superficial lesions, worse in immunosuppressed</td>
</tr>
</tbody>
</table>

### Food Poisoning/Enteritis - Shigella

<table>
<thead>
<tr>
<th><strong>• General Characteristics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>– Gram negative non-lactose fermenting rod, does NOT produce H₂S</td>
</tr>
<tr>
<td>– Facultative anaerobe</td>
</tr>
<tr>
<td>– nonmotile – spreads by actin tails</td>
</tr>
<tr>
<td><strong>• Pathogenesis</strong></td>
</tr>
<tr>
<td>– Spread by food, fingers, flies, feces</td>
</tr>
<tr>
<td>– Escapes phagolysosome and destroys host cell</td>
</tr>
<tr>
<td>– Shigatoxin - Necrotizing exotoxin causes mucosal necrosis</td>
</tr>
<tr>
<td>– fibrinosuppurative exudate</td>
</tr>
<tr>
<td>– Spreads to lymph nodes, but NO bacteremia</td>
</tr>
<tr>
<td>– Highly virulent - &lt;200 bacteria cause infection</td>
</tr>
<tr>
<td>– Classical dysentery - bloody diarrhea with inflammatory cells</td>
</tr>
</tbody>
</table>

### Food Poisoning/Enteritis - Yersinia enterocolitica

<table>
<thead>
<tr>
<th><strong>• E. coli types</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>– <strong>Enterotoxigenic (ETEC)</strong> - enterotoxin-producing strain. Causes watery diarrhea: LT tox (cAMP), ST tox (cGMP)</td>
</tr>
<tr>
<td>– <strong>Enterohemorrhagic (EHEC)</strong> severe bloody colitis virotoxin-producing strain (mainly O157:H7). HUS. Found in Raw meat!</td>
</tr>
<tr>
<td>– <strong>Enteropathogenic (EPEC)</strong> – effacement of microvilli</td>
</tr>
<tr>
<td>– <strong>Enteroaggregative (EAEC)</strong> - primarily pediatric diarrhea in impoverished nations</td>
</tr>
</tbody>
</table>

### Food Poisoning/Enteritis

<table>
<thead>
<tr>
<th><strong>• E. coli</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>– Gram negative rods</td>
</tr>
<tr>
<td>– EMB or McConkey Agar</td>
</tr>
<tr>
<td>– Lactose fermenting (coliform)</td>
</tr>
<tr>
<td>– Some strains have flagella</td>
</tr>
<tr>
<td><strong>• Causes:</strong></td>
</tr>
<tr>
<td>– K1 type causes neonatal meningitis</td>
</tr>
<tr>
<td>– Gastroenteritis, HUS, UTI, pneumonia.</td>
</tr>
</tbody>
</table>
**Food Poisoning/Enteritis**
- **Vibrio cholerae**
  - Gram negative “comma shaped” rod
  - Same disease as ETEC but more severe
- **Pathogenesis**
  - Enterotoxin that ADP ribosylates a stimulatory G
  - Protein causing secretory diarrhea
- **Clinical**
  - Copious diarrhea – up to 20L / day
  - Rice water stools
  - Shock from isotonic fluid loss if not rehydrated

**HUS, E. coli O157:H7**
- Shiga-like toxin of O157H7 (uncooked beef)
  - Endothelial damage at arteriole-capillary junction
  - Glomerular thrombotic microangiopathy: platelet-fibrin micro thrombi
  - Splitting of glomerular capillaries due to subendothelial swelling
  - Interlobular arteries: fibrinoid necrosis, subintimal fibrin deposits
- **Primarily in children (25% go to Renal failure)**
  - Immediate: nausea, abdominal cramping, fever
  - 3d: dark urine, hematuria, dark stools
  - DIC: elevated D-dimer, schistocytes, thrombi
- **Adult: TTP**

**Salmonella Typhi**
- **Salmonella Typhi**
  - G- bacillus; humans are only known host
  - fecal-oral transmission; 1-2 wk. incubation
  - facultative intracellular parasite
  - disseminates, causes typhoid fever
  - asymptomatic carrier state possible (gallbladder)
  - Invasive, “rose spots” on chest + abdomen
  - hepatosplenomegaly, invasive mucosal lesions
  - lymphoid tissue tropism
  - widespread mononuclear phagocytic involvement (wk 2)
  - typhoid nodules throughout immune tissue (includes liver), Peyer’s patches enlarge and later ulcerate

**Clostridial Diseases**
- **Clostridium perfringens, Clostridium septicum**
  - Cellulitis and gas gangrene, uterine myonecrosis (illegal abortions), food poisoning, tissue death allows growth (anaerobes)
  - Cellulitis: foul odor, thin discolored exudate, rapid and large tissue destruction, granulation tissue at borders, tissue necrosis disproportionate to nutrophil presence
  - Gas Gangrene: marked edema and enzymatic necrosis of muscle cells, extensive fluid exudate, large bulla that rupture, inflamed muscles soft, blue-black, friable, and semifluid, myonecrosis and hemolysis

**Clostridial Diseases**
- **Clostridium tetani**
  - Proliferates in puncture wounds/umbilical stump of newborns, convulsive contractions of skeletal muscles
- **Clostridium botulinum**
  - Proliferates in non-sterile canned foods, elaborates neurotoxin blocking ACh release, severe paralysis of respiratory and skeletal muscles
- **Clostridium difficile**
  - Pseudomembranous colitis, often nosocomial, seen in debilitated patients and those on long term broad spectrum antibiotics

**Rickettsia**
- Intracellular infection of endothelial cells with perivascular lymphocytic infiltrate (“perivascular cuffing”)
- obligate intracellular bacteria that can be found in ticks, mites, fleas, or lice, acquired by accidental exposure usually
- Eschar- dark, swollen, crusted lesion at inoculation site
- rash, small vessel vasculitis
- microthrombi, focal ischemia, or hemorrhage; also hypovolemic shock with peripheral edema possible
- lyse endothelial cell (typhus group) or spread cell to cell (spotted fever group)
- no exotoxins and no endotoxins
- Diagnosis: immunostaining of organisms or antirickettsial serology
**Rickettsia**

- **Epidemic Typhus** (*R. prowazekii*): head lice (prisons, concentration camps, refugee camps)
  - Centrifugal rash followed by CNS involvement - apathy, dullness, stupor, and coma
  - High fever, chills, cough, rash, severe muscle pain, sensitivity to light, delirium
- **Spotted Fever Group**
  - Rocky Mountain Spotted Fever - *R. rickettsia*
    - Tick bite (ixotid or hard ticks – American Dog Tick, Rocky Mountain Wood Tick)
    - Fever, nausea, vomiting, headache, muscle pain, anorexia
    - Hemorrhagic rash extends over entire body, including palms and soles; rare eschar - rash does not occur in all individuals
    - Cause of death - pulmonary edema (untreated - 30% mortality)

**Lyme Disease**

- Stage 1 (gone in 4-12 wks) – spirochetes spread in dermis, bulls eye rash (erythema chronicum migrans) characterized by edema and lymphocytic plasma cell infiltrate, fever, lymphadenopathy.
- Stage 2 (early disseminated stage) – organisms spread hematogenously, secondary skin lesions, meningitis with cranial nerve involvement (CSF is hypercellular with lymphocytes and anti-spirochete IgG), lymphadenopathy, migratory muscle and joint pain.
  - Early lyme arthritis resembles early RA with villous atrophy, lining cell hyperplasia, and lymphocytes and plasma cells in the sub-synovium.

**Rickettsia/ Ehrlichiosis**

- **Ehrlichiosis** (*E. chaffeensis* or *Anaplasma phagocytophilum*): tick vector in US
  - Similar symptoms to Rocky Mountain Spotted Fever, but rash rare, less prominent; no eschar
  - Infects neutrophils or monocytes
  - Characteristic cytoplasmic inclusions (morulae) – masses of bacteria shaped like mulberries
- **Scrub typhus** (Spotted Fever Group)
  - Endemic in Far East, China, India
  - Transmitted by chiggers
  - Rash transitory or absent
  - May be a prominent lymphadenopathy

**Pet-Associated Diseases**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>Animal bites, scratches (cat) Rapidly developing cellulitis, abscesses &amp; sepsis</td>
</tr>
<tr>
<td><em>Bartonella henselae</em></td>
<td>Cat scratches Self-limited – papule develops 3-10 days &amp; fever &amp; lymphadenopathy develop 2 weeks after contact, Immunocompromised: Bacillary angiomatosis-proliferation of small blood vessels</td>
</tr>
<tr>
<td><em>Leptospirosis</em></td>
<td>Common in dogs; organism secreted in urine – campers and swimmers Self-limited, febrile illness with biphasic fever and meningitis; conjunctival irritation and hyperemia; lymphocytic atypical meningitis; jaundice, bleeding, and renal failure (Weil’s disease) – spreads in liver, spleen, kidneys, and CNS with little cellular reaction</td>
</tr>
</tbody>
</table>

**Pet-Associated Diseases**

<table>
<thead>
<tr>
<th>Pathogen</th>
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<tbody>
<tr>
<td><em>Toxoplasmosis</em></td>
<td>Shed in feces of cats Normally subclinical or mild lymphadenopathy, serological titers confirm previous infection and protective immunity; Encephalitis in immunocompromised; TORCH in infants, TRANSPLACENTAL – chorioretinitis and blindness in 3rd trimester 25% fatality in 1st Trimester</td>
</tr>
<tr>
<td><em>Chlamydia psittaci</em></td>
<td>Inhalation of dust-borne excretia from birds Enters through respiratory tract and causes patchy inflammation of the lungs; interstitial edema, hyperemia, and mononuclear infiltrate</td>
</tr>
<tr>
<td><em>Rabies Virus</em></td>
<td>Saliva of infected animal (dog, raccoon, bat) CNS-hydrophobia; lesions characterized by presence of Negri bodies in nerve cells; only diagnosed by direct exam, treat with vaccine and Ig; vaccine for high-risk</td>
</tr>
</tbody>
</table>
### B. anthracis (Anthrax)
- Gram-positive, encapsulated, spore-producing rod
- Transmitted through contact with animal products (sheep, goats)
- 2 disease forms:
  - **Cutaneous disease** – eschar formation, painful lymphadenitis
  - **Pulmonary disease** – pneumonia with serofibrinous exudation, septicemia, possible DIC (woolsorter’s disease)
- **Virulence factors:** antiphagocytic activity (capsule), edema factor, cytotoxic factor; causes leukopenia
- Stable in environment, highly virulent -> bioterrorism
- Treatment: penicillin, doxycycline, vaccination available

### L. monocytogenes (Listeriosis)
- Small gram-positive rod; motile; facultative psychrophile (likes cold)
- Transmitted by contact with infected animals, uncooked food, unpasteurized milk
  - Also, maternal-fetal transmission
- **Causes:**
  - Spontaneous abortion
  - Neonatal sepsis with meningitis
  - Meningitis in adults if immunosuppressed
- Exudative meningitis in adults -> can see gram positive rods in CSF
- Need intact cell-mediated immunity to fight infection

### Mycoplasma
- Cell membrane contains sterols; no cell wall
- **Pneumonia** (walking/atypical) – *M. pneumoniae*
  - Xray looks worse than patient presents, high IgM titer.
  - MC pneumonia in school children/young adults, military.
- May have **hemorrhagic bullous myringitis**
- **Cold agglutinin**Æ immune hemolytic anemia
- **Diffuse, patchy inflammation in interstitial areas of alveolar walls, intraalveolar hyaline membrane**
- **Urethritis** – NGU; *Ureaplasma urealyticum, M. hominis*

### Mycobacteria
- Acid fast, mycolic acid in cell walls, intracellular
- Glycolipids prevent phagolysosomal membrane fusion
- **M. tuberculosis** - *caseating granulomas*
  - Histocytes (epithelioid cells), Langhans giant cells, peripheral collar of fibroblasts and lymphocytes
  - Granuloma formation – macrophages unable to kill bacteriaÆ persistent infectionÆ recruits T,1 cellsÆ secrete IFNγÆ activate epithelioid macrophages
- **PPD/Tuberculin test** – test for infection; Type 4 hypersensitivity reaction

### M. Tuberculosis
- **Primary** – localized; Ghon focus (TB granuloma) in periphery of lower upper lobes or upper lower lobes with hilar/lobar lymph nodes (Ghon complex)
- **Secondary** – cavitary lesions in apical lobes (↑ O2 tension); may rupture into bronchi; fever, night sweats, weakness, anorexia, weight loss, productive cough, blood in sputum
- **Tertiary** – extension in lung and to opposite lung; bacteremiaÆmiliary TB may spread to cervical nodes, meninges, kidneys, adrenal glands, bones (Pott’s disease in spinal cord), uterus, small intestine

### Other Mycobacteria
- **M. kansasii or MAC** – pulm. disease; associated w/AIDS, chronic bronchitis and emphysema
- **M. bovis** – unpasteurized milk, some pulmonary infections
- **MAC & M.scrofulaceum (kids)**Æ cervical lymphadenitis
- **M. leprae**Æ Leprosy (Hansen’s disease); cool areas
  - **Tuberculoid** – high immunity, form granulomas, self-limited;
  - **Lepromatous** – low T-cell immunity, organisms proliferate in macrophages; contagious and lethal
Infectious STDs - Chlamydia

- **Clinical Features:**
  - Reactive arthritis (Reiter's), conjunctivitis, nongonococcal urethritis, PID.
  - #1 STD in U.S. ½ asymptomatic.
  - #1 worldwide cause of preventable blindness (Trachoma; casual spread). Congenital inf. causes inclusion conjunctivitis (benign, self-limited), trachoma, & infant pneumonia.

- **Micro:** G-; Obligate intracellular organism of mucosal epithelium; lacks muramic acid and peptidoglycan wall.

- **Path:**
  - Two forms:
    - Elementary body (infectious, enters by endocytosis)
    - Reticulate body (replicative form). Enhances HIV transmission.
  - Diagnosis: cytoplasmic inclusion bodies on Giemsa stain or fluorescent antibody stained smear; Urine DNA amplification tests.

- **Treatment:** erythromycin or tetracycline.

---

Infectious STDs - Neisseria

- **1) Neisseria gonorrhoeae**—Gonorrhea
  - Clinical Features:
    - Urethritis, cervicitis, PID, prostatitis, epididymitis, septic arthritis, creamy purulent discharge.
    - 2nd most common STD. #1 cause of septic arthritis in young, sexually active people.
  - **Micro:** Pyogenic, encapsulated, G- diplococcus.

- **2) C. donvani**—Granuloma Inguinale
  - Chronic STD with ulcerating and granulating lesions of genital skin and mucosa

- **Path:** Antigenic variations allow evasion and re-infection; Adhesins and pili allow it to bind to epithelium; IgA protease stops Abs; Capsule inhibits phagocytosis.

- **Diagnosis:** Gram stain and see diplococci within the WBCs.

- **Tx:** Ceftriaxone; add doxycycline or azithromycin for Chlamydia

---

Infectious STDs - Trichomonas vaginalis—Trichomoniasis

- Clinical Features:
  - Women: vaginitis, copious secretions, strawberry mucosa. Men: asympt. or nongonococcal urethritis
  - **Micro:** Flagellated protozoan which occupies the vagina & urethra.

- **Path:** mild tissue rxnÆ2° bact. infectionÆpurulent urethritis & mucosal papules (strawberry muc.). Trophozoite growth results in profuse, watery, leukorrhoeic discharge with vulvovaginitis.

- **Dr:** Motile, turnip-shaped trichomonads on fresh prep of discharge.

- **Condylomata acuminata**—genital warts, koilocytes, HPV 6/11.

- **Haemophilus ducreyi**—Chancroid

- (painful, soft genital ulcer) at site of inoculation, inguinal adenopathy. Ulcer facilitates HIV transmission. Underdeveloped Countries.

---

Infectious STDs - Syphilis

- **Treponema pallidum**—Syphilis

- **Micro**
  - G- spirochete
  - Produces no toxins

- **Path**
  - 1°: local reaction
    - no toxinsÆdamage from immune rxn.
  - 2°: BacteremiaÆsystemic manifestations
    - (maculopapular rash including palms and soles)
Infectious STDs - Syphilis

- **Path cont’d**
  - 3°: Cardio most affected
    - Aortitis (vasa vasorum destroyed → obliteratorative endarteritis (tree-barking) → damage prox aorta & root → aneurysms & dissections)
  - Gummas (liver, bones, testes, skin) from DTH (Type IV) → w/central necrotic debris bordered by palisading mphages and fblasts. No treponemes.
  - Neurosyphilis: Tabes dorsalis (post. column → sensory loss → charcot joints); general paresis; Argyll Robertson Pupils (midbrain lesions; pupil constricts w/ accommodation but not w/light)

Infectious STDs - Syphilis

- **Clinical Features:**
  - **Primary:** Painless, hard chancre that appears 3-6 weeks after inoculation & lasts one month. VDRL and Anti-treponemal antibodies are neg. but organisms can be extracted from lesions
  - **Secondary:** ~6 weeks after 1° lesion heals; fever, condyloma lata (elevated broad plaques) on penis/vulva, lymphadenopathy, skin rashes (esp. palms and soles), VDRL and Anti-trep antibodies are positive, organisms can be extracted from lesions.
  - **Tertiary:** After asymptomatic latent period (>5 years).
    - Gummas; Neurosyphilis; Argyll Robertson pupils (pathognomonic for 3°); Tabes dorsalis; aortic aneurysm and dissection. general paresis. VDRL and Anti-trep abs are pos but organisms can’t be found.

Infectious STDs

- **Congenital Syphilis (TORCH)**—Treponemes cross BBB. Periosteal inflammation → Saber shins (bowing), saddle nose, eighth nerve deafness*, Hutchinson’s teeth*, and interstitial keratitis*. *Hutchinson’s Triad

  - **Herpes Simplex Type 2: Genital Herpes**
    - **Clinical:** painful penile, vulvar, or cervical ulcers; Congenital (TORCH) syndrome → generalized lymphadenopathy, splenomegaly, corneal lesions, CNS damage (deafness, ataxia)
    - **Micro:** Encapsulated virus w/ ds-DNA.
    - **Path:** Cell destruction → separation of epithelium → vesicles. Viral assembly forms intranuclear inclusions. Viral proteins fuse cells forming multinucleated giant cells. Scrapings reveal intranuclear inclusion-bodies within multinucleated giant cells (TZANCK PREP).

Measles/Rubella

- **Measles** → paramyxovirus
  - Highly contagious- epidemics
  - Cough, coryza conjunctivitis
  - Macular papular rash that coalesces
  - Koplik spots → red spot w/bluish-white center near Stensen’s duct
  - Warthin-Finkeldy multinucleated giant cell - pathognomonic!!
  - Subacute sclerosing panencephalitis (Dawson encephalitis) is a potential sequela

- **Rubella** → togavirus
  - Infections of children mild but part of congenital TORCH syndrome
  - Transmission through placenta
  - Congenital → heart and major vessel defects, ocular lesions, deafness, microcephaly, mental retardation, growth retardation

Mumps

- **Mumps** → paramyxovirus
  - Dz of parotid gland
  - Can affect pancreas, ovaries, testes → hemorrhage into testis can cause permanent damage and sterility- usually unilateral
  - Intense interstitial edema and monocytic infiltrate

  - **Vaccination MMR for all three at >12 months and again at 4-6 years of age**

Herpes – HHV6 and 8, Herpes Fun Facts

- **HHV 6** → Roseola; begins as a high fever; when the fever disappears, a red rash develops; mono-like in adults.

- **HHV8** → Kaposi’s sarcoma; cancer of lymphatic endothelium forming blood-filled channels; associated with AIDS as an opportunistic infection; lesions occur on the skin, mouth, GI tract, and respiratory system. Patches are pink to red to purple. Initially difficult to discern from granulation tissue. Later lesions become raised plaques with dilated jagged vascular channels.

  - All herpesviruses are DS linear DNA
  - All have the characteristic multinucleate giant cells and intranuclear Cowdry type A inclusion bodies.
Herpes
• HSV1: gingivostomatitis (cold sores); HSV2: genital lesions; characteristic multinucleated giant cells with intranuclear inclusions – TZANK prep.
• Virus enters skin; infects and becomes latent in nerves.
• Can also cause keratitis, encephalitis, and disseminated disease (immunocompromised); keratitis can lead to corneal blindness.
• One of the TORCH diseases – lymphadenopathy, splenomegaly, necrosis, corneal lesions, CNS damage.

Varicella-Zoster
• Transmitted by aerosols then viremia leads to rash beginning on face and spreading to rest of body, including mucous membranes
• Vesicles resemble “dew drop on rose petal”, and occur in crops; itch when healing.
• Latent in neurons of the DRG.
• Shingles occurs from reactivation of VZV and is distributed along a sensory dermatome; painful, vesicular rash; rare interstitial pneumonia, encephalitis, or necrotizing lesions.

Cytomegalovirus
• Cytoplasmic “owl’s eye” inclusions; spread by resp. drop.
• Most people get an asymptomatic infection.
• Other possible infections – CMV mononucleosis; reactivation in AIDS (CMV retinitis); reactivation in bone marrow transplant (CMV pneumonitis); in AIDS patients accompanied by PCP.
• Congenital infection (TORCH) – hemolytic anemia, jaundice, thrombocytopenia purpura, hepatosplenomegaly, deafness, chorioretinitis, brain damage, encephalitis.

EBV
• Mononucleosis – self limited; pharyngitis, fever, chills, sweats, headaches, swollen lymph nodes, and hepatosplenomegaly with risk of splenic rupture
• Spread thru saliva; causes polyclonal activation of B-cells (attaches to CD21)
• Atypical lymphocytes are T cells; absolute lymphocytosis
• Heterophile antibodies useful – MONOSPOT TEST (detect Ig against Horse RBCs)
• Associated with Burkitt’s Lymphoma and nasopharyngeal carcinoma.

Lower Respiratory Tract Infections
• Influenza, Parainfluenza, Respiratory Syncytial Virus
  – Spread by aerosolized droplets
• Influenza
  – orthomyxovirus with single strand negative (SS-) RNA
  – hemagglutinin promotes viral entry
  – neuraminidase promotes release of viral particles
  – Antibodies to hemagglutinin and neuraminidase are protective but antigenic shift and drift result in subsequent infections
  – Virus grouped into types A, B, C (type A responsible for pandemics and epidemics)
• Pathology: Interstitial Pneumonia
  – Mucosal hyperemia with lymphomonocytic and plasmaocytic infiltration of submucosa
  – Mucosal hypersecretion -> can lead to Secondary Bacterial Infections (usually Staph Aureus). Major cause of mortality

Lower Respiratory Tract Infections Cont’d
• Parainfluenza Paramyxovirus, single strand negative SS- RNA
  – Mostly infects children, causing Croup (laryngotracheobronchitis) in young children
    • Croup is a harsh barking cough usually accompanied by inspiratory stridor
    • Inspiratory stridor is due to airway obstruction from submucosal edema in the trachea
• Respiratory Syncytial Virus Paramyxovirus, SS- RNA
  – Most common cause of viral pneumonia and bronchiolitis in young children and common cause of death in infants 1-6 mos.
  – Healthy adults are protected by IgA in the airways
  – Fusion proteins from the virus cause formation of multinucleate giant cells in respiratory tissue.
### Rotavirus
- Encapsulated, dsRNA virus
- Common cause of gastroenteritis in children aged 6-24 months; causes vomiting and watery diarrhea
- Selective infection & destruction of mature enterocytes in small intestine, sparing crypt cell
- ↓ Absorption of nutrients → osmotic diarrhea and dehydration
- Outbreaks in day-care centers, hospitals
- Highly infectious: minimum infectious dose just 10 particles
- Immunity transferred through antibodies in maternal milk, so infection common at weening

### Norwalk
- ssRNA virus
- Causes gastroenteritis with watery diarrhea, nausea, vomiting, abdominal pain
- Transferred via food, water, person-person; extremely sturdy virus, difficult to kill
- Occur in epidemics, common on cruise ships
- 1-2 day incubation, symptoms lasting 12-60 hours

### Polio & Coxsackievirus (Enteroviruses)
- Enteroviruses → small, +sense single stranded RNA
- Transmitted by fecal/oral route, respiratory secretions
- Can be asymptomatic, or cause mild respiratory infection, rash, aseptic meningitis, some assoc w/ severe complications
- May be related to onset of type 1 diabetes
- Coxsackie A – Hand Foot & Mouth Disease and Herpangina
  - Hand foot & mouth – fever/malaise, then 2 days later painful oral vesicles and maculopapular rash on hands & feet
  - Herpangina – fever, sore throat, red-based vesicles on back of throat
- Coxsackie B – Myocarditis, Pericarditis
  - Myocarditis – lymphocytic infiltrate & associated myocyte injury

### Polio & Coxsackievirus (Enteroviruses)
- Poliovirus
  - Initial replication occurs in peyers patches & tonsils
  - Asymptomatic, or causes a mild febrile viral illness in most people, can also cause aseptic meningitis w/ complete recovery
  - In 1% of cases, spreads to blood and then across the blood-CNS barrier to motor neurons in the anterior horn of spinal cord → causes paralysis (pain, weakness, LMN signs)
  - Vaccinations
    - Salk – inactive virus injection, no risk of vaccine-associated disease
    - Sabine – oral attenuated virus, longer duration of immunity and “free immunization” of others by virus shed in stool, but carries risk of vaccine associated polymyelitis in immunocompromised

### Parvovirus
- Parvovirus B19 (small, single stranded DNA virus)
  - Respiratory transmission, children age 4-12, 20% asymptomatic
  - Fifth disease (Erythema Infectiosum)
  - Fever & “slapped-cheek” rash; lacy red rash on trunk & limbs that may itch, no longer contagious by the time the rash occurs
  - Associated with aplastic anemia in patients with sickle cell, chronic diseases, or immunosuppression
    - Virus interferes with RBC production in the bone marrow
    - Pink intranuclear inclusions present in RBC precursors
    - Pregnant mothers can pass the virus to the fetus, resulting in severe anemia with fetal hydrops

### Adeno, Rhino, & Coronavirus
- Infection confined to upper respiratory tract – “common cold”
  - Virus prefers cooler temperatures
- Rhinovirus – single stranded +sense RNA, >100 serotypes
  - Cause >60% of common cold
  - Virus binds to ICAM-1 → infects humans and higher primates that have ICAM-1 on their epithelial cells
  - Hypersecretion due to bradykinins and inflammatory response
- Coronavirus – single stranded +sense RNA
  - 2nd most common cause of common cold, profuse nasal discharge
- Adenovirus – double stranded DNA
  - Pharyngitis, fever, conjunctivitis, keratoconjunctivitis (“pink eye”)
  - Can progress to lower respiratory tract pneumonia in children
  - Smudge cells and Cowdry type A intranuclear inclusion bodies
**West Nile, Dengue**

- RNA (Single-stranded + linear)-Flavivirdae viruses
- Spread by **Mosquito vector**, infecting humans and birds
- **Dengue Fever**
  - Primarily in tropics, some in SW U.S.
  - “Break-bone fever”- b/c of backache, joint pain, and severe headache. PAINFUL FEVER!
  - Serotype 2 leads to **Dengue Hemorrhagic fever**
    - Causes hemorrhage or shock, especially in children
- **West Nile Virus**
  - Birds are major reservoir, humans are accidental hosts
  - Broad geographical distribution
  - Sx: Most are asymptomatic, some develop headache, fever, and maculopapular rash;
  - Meningitis/encephalitis/meningoencephalitis in 1:50 of clinically infected individuals
  - Immunosuppressed and the elderly at greatest risk

**Smallpox, yellow fever**

- **Smallpox**
  - Family of poxviridae (Variola major and minor)
  - Only infects humans-NO animal reservoirs
  - HIGHLY contagious, spread person to person
  - No known treatment w/ mortality of 30%
  - Clinical presentation
    - Sx:
      - Synchronous
      - Centrifugal spread (mostly face and palms); fever
- **Yellow fever**
  - RNA Flavivirus (yellow fever virus), arbovirus
  - Transmitted by the *Aedes* mosquitoes. Monkey or human reservoir
  - Clinical Presentation
    - Hepatitis and jaundice (may see Councilman bodies in liver)
    - Fever, backache, nausea, and vomiting

**Ebola and Hanta (Hemorrhagic Fevers)**

- **Ebola** – negative sense ssRNA, Filovirus; no vector definitively identified, monkeys?
  - Person to person; nosocomial in endemic areas; isolation is essential
  - Hemorrhagic manifestations from many organ systems, hepatic especially; visceral organ necrosis
  - Die secondary to hemorrhage, massive fluid loss, shock and DIC.
- **Hanta** – negative sense, ssRNA, Bunyavirus, very rare in US
  - Inhaled rodent urine and feces, Southwest US
  - Acute hemorrhagic pulmonary syndrome, mortality 50%
  - Fever, hemorrhage, ARDS, DIC

**Actinomyces and Nocardia**

- Nocardia and Actinomyces are bacteria that act like fungi
- Exhibit branching and Mycelial Network
- Nocardia infects the immunosupressed
  - 1) Pulmonary with single or multiple necrotizing abscesses.
  - 2) Disseminated: Meningitis
  - 3) Skin Lesions

**Nocardia & Actinomycoses Cont.**

- Actinomyces (strictly anaerobic, lives in devitalized tissue)
  - Chronic suppurative infection. SULFUR GRANULES in exudate.
  - Three disease forms: Cervicofacial, Abdominal, thoracic
    - Cervicofacial = most common form. Begins in Gingiva.
    - Invasive Lesions which perforate and form abscesses.
      - Central suppurative necrosis surrounded by granulation tissue and fibrosis
    - Abdominal = Inversions of the Intestinal mucosa
    - Thoracic = Lung abscesses, empyema

**Mucormycosis & Aspergillus**

- Mucormycosis: Irregular nonseptate hyphae w/ wide angle branching
  - Pathogenesis: Invasion of arterial wall w/ hemorrhage and thrombosis
- 3 primary sites:
  - Rhinocerebral (Diabetic ketoacidosis): local tissue necrosis.
  - Lung: Hemorrhagic pneumonia
  - GI involvement with severely malnutrition in children
  *Occurs in immunosupressed, diabetic ketoacidosis
  *Often Nosocomial
### Aspergillus
- Septate hyphae with narrow angle branching:
  - Pathology: Same as mucormycosis. Also has aflatoxin (carcinogen/Liver cancer)
- Allergic: Alveolitis (III, IV), asthma (I)
- Colonizing: *Fungus Balls* in pre-existing cavities (minimal invasion)
  - Associated with recurrent hemoptysis
- Invasive: necrotizing pneumonia, sepsis (esp. heart valves, brain, kidney)
  - Immunosuppressed and debilitated hosts

### Candida
- Morphology
  - pseudohyphae and budding yeasts
- Path
  - Phenotypic switching
  - Adhesion proteins (yeast bind manose, hyphae bind Fc)
  - Enzymes and adenosine (blocks oxygen radical formation)
  - Stimulates TH1 response
- Presents
  - Thrush, esophagitis, vaginitis, coetaneous, invasive, endocarditis,
  - Normal flora
  - Superficial infx in healthy, disseminated in immunocomp.
    - Newborns, AIDS, Diabetics

### Cryptococcus and Pneumocystis
- Cryptococcus neoformans
  - Path: encapsulated yeast with 3 virulence factors
    - Polysaccharide capsule, melanin production, enzymes
    - Capsular polysaccharide stains red, Agglutinates latex
  - Found in soil and pigeon droppings
  - Primary infx in lungs, major lesion in CNS
- Pneumocystis Jiroveci (PCP)
  - Path: yeast, cyst-forming lesions. Wide-spread pulmonary infiltrates on CXR
  - Affects immunocompromised (AIDS)
  - Toluidine blue stain after lung lavage shows organism
  - TMP/SMX treatment and prophylaxis.

### Histoplasmosis
- Thermally dimorphic fungus in bat and bird droppings
  - Endemic to Ohio and Mississippi river valleys and Caribbean;
    - Microconidia are the infectious form
  - Yeast enters macrophages by induced phagocytosis
    - Proliferates in phagolysosome and lyses host cell
    - T-cells recognize antigens and induce granulomatous response
  - Presentation depends on host immune response
    - Immunocompetent host: epithelioid caseating granulomas;
      organization and concentric calcification; asymptomatic, but coin lesion on CXR
    - Chronic infection: clinically similar to TB with less cavitation
    - Fulminant disseminated: only in immunocompromised;
      granulomas absent; focal accumulations of yeast-filled Mo’s
    - Methenamine silver staining of yeast in affected tissue

### Blastomycosis
- Thermally dimorphic soil inhabitant in *central/southeast US*
  - Infective conidia transform into round, thick-walled yeast exhibiting broad-based budding
- Macrophages have limited ability to phagocytose
  - Persistence of yeast leads to continued neutrophil recruitment
- Abrupt illness with tuberculosis-like symptoms
  - Nodular or miliary infiltrates with lobar consolidation on CXR
  - Suppurative granulomas, most frequently in upper lobes
  - Can disseminate to skin, causing raised, ulcerating verrucous lesions with epithelial hyperplasia; can be confused with squamous cell carcinoma
  - Widespread dissemination in immunosuppressed

### Coccidioidomycosis
- Thermally dimorphic soil inhabitant of *southwest US*
  - Arthroconidia infect almost everyone; clinical illness in 10%
  - High infectivity requires careful handling by lab workers
- Inhibition of fusion of phagosome and lysosome; T-cell stimulation results in granulomatous inflammation
  - Thick-walled, non-budding spherules within macrophages and giant cells
  - Rupture releases non-infectious endospores, stimulating a superimposed pyogenic inflammation
  - San Joaquin Valley Fever: fever, cough, pleuritic pain,
    - erythema nodosum or erythema multiforme
  - Rare dissemination to meninges or skin; pyogenic inflammation may dominate, especially in immunosuppressed
Protozoa

• Babesiosis
  – Similar to malaria, but found in the US
  – Protozoan transmitted by deer ticks (also carry Lyme disease)
  – Sx: Fever, hemolytic anemia, worse in debilitated and splenectomized

• Trichomoniasis
  – Trophozoites—turnip-shaped motile organisms
  – Colonize vagina and male urethra – vaginitis, cervicitis, urethritis
  – No tissue invasion with little inflammatory rxn, green frothy discharge
  – “Strawberry mucosa”, mixed cell infiltrate

• African Sleeping Sickness (Trypanosomiasis)
  – Vector: Tsetse fly; Clinical: intermittent fevers, lymphadenopathy, splenomegaly, leptomenigitis, cachexia, death
  – Organism growth actually stimulated by IFN-gamma; tissue destruction from antigen/antibody complex deposition
  – Red, rubbery chancre at site of infection; ulcer & mononuclear infiltrate

• Chaga's Disease (T.Cruzi)
  – vector: kissing bug; most common cause of heart failure in Brazil
  – chagoma at site of infection; infects macrophages; penetrates smooth, skeletal, and cardiac muscle
  – Acute: intracellular pseudocysts, fever, dilated cardiomyopathy, arrhythmias
  – Chronic: cardiac damage due to Antibody-T cell cross reaction

· Protozoa

• Cholera
  – Vector: bacterium spread by water and contaminated food
  – Clinical: explosive watery diarrhea, vomiting, dehydration

• Giardia
  – Transmission via cysts in contaminated water and fecal-oral; Not killed by chlorine
  – Trophozoites resemble “cartoon ghost”

• Cryptosporidiosis (Cryptosporidium parvum)
  – Oocytes: infectious, not killed by chlorine
  – Sporocytes: attach to brush border of apical epithelium
  – Clinical: malabsorption, secretory diarrhea, vomiting (3-14 days); increased severity in immunosuppressed
  – Organisms infect Peyer’s patches and macrophages, CD-4+ immunity needed to control parasites

• Balantidiasis
  – Cysts are infectious through contaminated food and water, common in tropics, pigs
  – Clinical: Persistent diarrhea, dysentery, weight loss

GI Protozoa

• Amebiasis (Entamoeba histolytica)
  – Infections cysts lyse colonic epithelium of cecum and ascending bowel → flask-shaped ulcers
  – Trophozoites invade the crypts of colonic glands, 40% penetrate portal vessels → liver abscess
  – Clinical: dysentery (in only 10%)

• Giardia (Giardia lamblia)
  – Transmission via cysts in contaminated water and fecal-oral; Not killed by chlorine
  – Clinical: diarrhea, steatorrhea, constipation, IgA Deficiency and the immunosuppressed are more susceptible (but not worse clinical disease)
  – Clubbing of villi, but no invasion of intestinal wall

Tissue Invaders

• Toxoplasmosis: Obligate intracellular protozoan, cat is definitive host; Opportunistic AIDS infection; Oocytes shed in cat feces, infectious after 24-48 hours, (scoop litter ASAP)
  – Fetus: chorioretinitis, damaging to heart, brain, lung development
  – Adults: follicular hypertrophy and lymphadenopathy

• Leishmaniasis: sandfly vector; visceral form via RES
  – Kala-azar; cutaneous form with ulcer and granulomatous reaction; mucocutaneous form – disfiguring lesion; diffuse cutaneous form

• Naegleria: water transmission; meningitis w/ death in kids (entry through cribiform plate), mimics meningococcus

• Acanthamoeba: meningitis in immunocompromised via hematogenous spread, sense of smell/taste altered
Trematodes

- Schistosomiasis – The life cycle involves fresh water snails, humans are affected when cercaria penetrate skin. Organisms migrate to portal vein and pelvic venous plexus. Immune response is granulomatous and eosinophilic with significant fibrosis (out of proportion to parasitic injury)
  - S. mansoni/japonicum → pipestem fibrosis → portal HTN
  - S. haematobium → hematuria and bladder obstruction → squamous cell carcinoma
- Liver flukes (clonorchiasis) – from poorly cooked fish.
  - In biliary tracts → portal fibrosis → cholangiocarcinoma

Malaria Life Cycle

- Sporozoites found in salivary glands of female Anopheles mosquito
- Sporozoites enter the blood when bitten and invade liver cells (thrombospondin, properdin) where they multiple rapidly forming many merozoites (asexual, haploid)
- Merozoites bind by a lectin like molecule to sialic residues on glycoprotein on RBCs
- The parasites grow within the RBC, hydrolyzing hemoglobin—trophozoite is the first stage in the RBC and is defined by a single chromatin mass
  - Detoxification of heme by forming paracrystalline precipitate (hemozoin) → Chloroquine inhibits this detoxification

Malaria cont’d.

- The next stage: The schizont has multiple chromatin masses, each of which develop into a merozoite. On lysis of the RBC the new merozoites infect additional RBCs
- Some parasites develop into gametocytes, instead of merozoites, and infect the mosquito when it takes its blood meal
- P. Falciparum causes more severe disease:
  - Can infect RBC of any age causing severe anemia
  - causes RBCs to stick together and stick to endothelial cells (sequestrin knobs bind ICAM-1; ischemia due to poor perfusion—cerebral malaria: 80% of death in children)
  - stimulates production of high levels of cytokines
- P. vivax and ovale form latent hypnozoites in hepatocytes

Malaria

- Sickle Cell Trait, β Thalassemia Minor, and Duffy Antigen absence (P. vivax only) may confer some immunity
  - Immunity may increase with repeated infections
  - HLA-B53 are resistant to P. falciparum because they present liver stage antigens to cytotoxic T cells that kill the infected hepatocytes
- P. Falciparum infection causes enlargement and pigmentation of the spleen and, with progression, the liver enlarges and becomes pigmented. With chronic infection the spleen becomes fibrotic and brittle. Hemolysis → hemoglobinuria (black water fever)
- Pigmented phagocytic cells may be found throughout the bone marrow, lymph nodes, and subcutaneous tissues, and lungs. The kidneys are often enlarged and congested with hemoglobin casts. Focal hypoxic lesions in heart due to anemia and stasis.

Cestodes

- Taenia solium – Ingestion of undercooked pork
  - Ingest cysticercus (larvae) → adult tapeworm in intestine
  - ingest eggs → cysticeri in brain → neurocysticercosis → hydrocephalus, focal neuro deficits
- Taenia saginata – ingestion of undercooked beef.
  - Tapeworm adheres to intestinal mucosa, no cysticercosis
- Echinococcus (E. granulosus, E. multilocularis) - canine Tapeworm. Often asymptomatic. Ingestion of eggs → hydatid cysts in liver, lungs, brain. Rupture of cyst → anaphylactic rxn. Must surgically remove w/o rupture

Echinococcus (E. granulosus, E. multilocularis) - canine Tapeworm. Often asymptomatic. Ingestion of eggs → hydatid cysts in liver, lungs, brain. Rupture of cyst → anaphylactic rxn. Must surgically remove w/o rupture

Nematodes

- Pinworms (Enterobius vermicularis)
  - ingestion of eggs, extruded from anus. Anal pruritis, scotch tape test.
- Whipworm (Trichuris trichiura)
  - ingestion of eggs → migration to colon → abdominal pain, diarrhea
- Hookworms (Necator americanus, Ancylostoma duodenale)
  - Seen in Southern U.S. Larvae penetrate toes → lungs (Loeffler pneumonitis) → cough and swallow → intestine (iron deficient anemia)
- Strongyloides – same as hookworms except life-threatening infection in immunocompromised
**Nematodes, cont’d**
- *Trichinella spiralis* – ingestion of improperly cooked pork
  - Penetrate tissue → hematogenous dissemination → encyst in muscle (increased CK, periorbital edema)
- **Arthropods**
  - scabies – in keratinized layer of skin, recur every 28 d.
  - head lice – 2° bacterial infection may be a complication

**Other Parasites**
- **Larval migrans**
  - Cutaneous larval migrans (Ancylostoma) – hookworms from dogs and cats, pruritic skin lesions
  - Visceral larval migrans (*Toxocara canis, cati*) – dog/cat ascaris, can result in widespread dissemination
  - Neural larval migrans (Balisascaris) – associated with wildlife (raccoons), severe CNS disease
- **Tissue Invaders**
  - Filariasis (*Wuchereria bancrofti*) – mosquito transmission, develop in lymphatics, elephantitis
  - Onchocerciasis – nematode transmitted by black flies, pruritic dermatitis, dermal nodules, retinal damage → blindness

**Rheumatoid Arthritis – General Features**
- Systemic autoimmune disease most commonly seen in 3rd-5th decades
  - Chronic course with episodic flare-ups
- Nonsuppurative, destructive joint lesions
  - Severe damage accumulates over decades
  - Cell-mediated synovial inflammation with Pannus
- May involve other parts of the body including skin (see nodules), blood vessels, heart, lungs, muscles, but usually not kidneys
  - Immune complex-mediated tissue damage

**RA – Pathogenesis**
- Characteristic lesions:
  - Pannus - proliferative response in synovial lining
  - Joint space loss - tissue destruction, chronic cell-mediated response, fibrosis, ankylosis
  - Juxta-articular bone erosions from cytokine-mediated stimulation of osteoclast activity
- **TNF & IL-1** induce resorption of cartilage and bone, enhance accumulation of leukocytes, stimulate fibroblast proliferation
- 80% have IgM antibodies to IgG (Rheumatoid Factor) - may be from plasma cells in synovium
- Triggered by exposure of immunogenetically susceptible host to arthrogenic microbial antigen
  - Associated with HLA-DR4 or DR-1
- Suggested theories:
  - Possibly EBV, parvovirus, mycobacteria, Borrelia, or mycoplasma
  - May be associated with autoimmunity to collagen II
- Lymphocyte and cell-mediated damage to synovium with chronic inflammation, proliferative response, and cytokine-mediated joint destruction

**RA – Pathogenesis**
- Rheumatoid Factor (RF) can form immune complexes, activate complement, and augment synovial inflammation as well as cause extra-articular disease
  - High RF titers may show vasculitis -> purpura, cutaneous ulcers
  - Also, see serosal disease
- MCP, PIP, ankles, feet, knees, upper spine commonly involved
  - Lumbosacral spine, hips spared
- **Rheumatoid nodules** - subcutaneous reaction with prominent histiocytes, lymphocytes, and plasma cells, similar to granuloma; not adjacent to involved joints; seen in 25% of patients
**RA – Pathogenesis Summary**

- Acute arthritis
  - autoimmune T-cell response (CD4-mediated)
  - induction of lymphocyte/macrophage/plasma cell response
  - chronic synovial tissue injury
  - pannus formation
  - joint/bone destruction

**RA – Pannus Formation**

- During acute attack synovium is edematous with inflammatory infiltrate, becomes hyperplastic
  - Lymphoid follicles may develop
  - Neutrophils accumulate in joint fluid (not synovial tissue)
- With time, tissue fibrosis develops
- Hyperplastic synovium fills joint space (pannus)
- Osteoclasts become activated, erode bone leading to cyst formation
- Joint space fills with pannus, fibrotic tissue
  - Can lead to ossification, ankylosis of bones and joints

**Rheumatoid Arthritis - Diagnosis**

- Most are nonspecific; **must have 7 criteria** (1-5 for at least 6 months)
  - Morning stiffness
  - Pain on motion or tenderness in at least 1 joint
  - Swelling of at least one joint
  - Swelling of at least one other joint, no period greater than 3 months without symptoms
  - Symmetrical joint swelling with simultaneous involvement of same joint of both sides
  - Subcutaneous nodules over bony prominences, on extensor surfaces, or in juxta-articular regions
  - x-ray change typical of RA

**Rheumatoid Arthritis – Diagnosis (cont’d)**

- RF factor positive
- Poor mucin precipitate from synovial fluid
- Characteristic histiologic changes in synovial membrane
- Characteristic histiologic changes in nodules showing granulomatous foci with central zones of cell necrosis
- Other associated syndromes:
  - **Felty’s syndrome** – RA, splenomegaly, neutropenia
  - **Caplan’s syndrome** – RA with pneumoconiosis

**RA – Clinical Features**

- More common in women – 3rd to 5th decade
- Chronic, episodic, relapsing/remitting, symmetrical joint destruction
- MCP,PIP,feet>wrists>ankles>elbows>knees>spine
- Lumbosacral spine, hips and DIP spared
- Radial deviation of wrists; ulnar deviation of fingers
- Constitutional symptoms - fever, weight loss, fatigue, lymphadenopathy
- Rheumatoid nodules (25%)- firm, nontender nodules in subcutaneous tissue – analogous to granulomas

**RA – Pathologic features**

- HLA-DR4 association
- Triggered by exposure to arthrogenic Ag – EBV?
- Rheumatoid factor – IgM autoantibody to Fc on IgG
  - Type III hypersensitivity reaction
- Lymphocyte and cell-mediated damage to synovium
  - Cytokine mediated joint destruction, and proliferative responses
  - Juxta-articular bone erosion – osteoclastic activity
- Pannus formation – hyperplastic synovium with lymphocytes, histiocytes and plasma cells
RA – Other Pathologic Features

- Felty’s syndrome- RA, splenomegaly, neutropenia
- Vasculitis- nail bed infarcts, purpura, cutaneous ulcer
- Severe vasculitis of eyes, lungs, heart
- High RF titers are associated with vasculitis
- Involvement of nerve-associated blood vessels leads to peripheral neuropathy

Juvenile Rheumatoid

- Juvenile Rheum. Arthritis: <16 yr. old; features of both RA and Lupus
  - Systemic disease (similar to lupus), symmetric arthralgias of large joints, erythematous rash, high spiking fevers
  - ANA positive, RF negative
  - No permanent joint deformities, usually does not continue into adulthood

Seronegative Spondylarthropathies: Ankylosing Spondylitis

- Autoimmune, seronegative synovitis
  - Affects adolescent males; 90% are HLA-B27 positive
  - Axial joints, especially sacroiliac and lower spine
  - ⅓ of cases also involve periphery
- Destruction of articular cartilage with inflammation of tendoligamentous insertions
- Fibrosis with ossification of ligaments and fusion of intervertebral joints leading to immobile “bamboo spine”
- Inflammatory compression of dorsal roots can lead to sensory disturbances
  - Charcot joints, paraesthesias, etc.

Seronegative Spondylarthropathies: Reiter’s Syndrome

- Autoimmune seronegative spondylarthritis triggered by prior GI/GU infection
  - Shigella, salmonella, yersinia, campylobacter, chlamydia
  - Presents 7-14 days after inciting infection
  - Males in 3rd and 4th decade; 80% are HLA-B27 positive
  - Asymmetric inflammation and stiffness of joints and tendinous insertions of lower back and lower extremities
  - Classic form also involves eye disease and urethritis
  - 50% have recurrent disease
  - Different bouts may involve different manifestations
  - Rarely cardiac conduction anomalies, aortic regurgitation

Other Non-RA Arthritis

- Juvenile RA: Large joint destruction, systemic symptoms more common, fever, glomerulonephritis, RF-, ANA+
- SLE: Type II/III, nonerosive synovitis, PMNs, HLA-DR2/3 Sero- Spondyloarth.: RF-, HLAB27, cell-med ♂, SI, eye
- Ankylosing Spondylitis: "triple A” Axial, Adolescent, Aortic reguriguation, Uveitis, Bamboo spine, SI
- Reiter’s Synd: “below-waist”; infection (GI or Chlamydia), arthritis( low back/SI/leg), conjunctivitis, males in 20-30s
- Psoriatic A: DIP, tendonitis “sausage joints”, SI, “pencil-cup” X-ray, conjunctivitis, iritis, ~5% of psoriatic patients

Other Infection-Related Arthritis

- Suppurative: febrile; red, swollen, hot “Don’t wait aspirate”
- S. aureus, Strep, gram – , H.Flu “less than 2”, salmonella (sickle), gonococcal (migratory, C5-C7 deficiency, ♀)
  - Hematogenous spread, increased sed rate
- Chronic: Lyme – migratory, large joints, mononuclear, onion skinning of arterial walls, papillary synovitis with fibrosis
- TB - weight bearing joint destruction and fibrous ankylosis
  - Potts disease - vertebræ
- Post-Strep: Rheumatic Fever, migratory, Jones criteria, 2-6 wks post infection, PMNs, TypeII/III
- Serum Sickness: joint similar to Post strep Type III
Other Non-RA Arthritis

- **Gout**: hyperuricemia, supersaturation of uric acid
  - uric acid crystal formation in joints – monosodium urate
  - foreign body reaction with giant cells, macrophages, lymphocytes
  - “tophus” cartilage/ligaments/tendons... may ulcerate
  - Joint damage may lead to chronic arthritis
- **Osteoarthritis**: progressive erosion of articular cartilage, 85% affected by age 65; typically no precipitating cause
  - Joint stress>chondrocytes supply inflammatory mediators, and proliferate> collagen and matrix degradation
  - narrowed joint space> reactive thickening of bone (HEBERDEN’S NODES in DIP -osteophytes)

Psoriatic Arthritis

- **Psoriatic**:
  - >10% of people with psoriasis, DIP of hands and feet (“sausage fingers”) affected first, asymmetric
  - Knees, hips, ankles, sacroiliac, spinal joints can also be affected
  - Extra-articular manifestations uncommon
  - Histologically similar to RA but joint destruction less common

Gout

- Middle aged men
- Episodic intense local pain- foot ankle, big toe(cooler areas)
  - Exacerbated by alcohol
- Tophus- pathognomonic lesion
  - mass of urate crystals surrounded by inflammation (macrophages, lymphocytes, foreign body giant cells),
  - usually on the ear, olecranon, patellar bursae, periarticular ligaments, connective tissue
- Joint aspiration- needle shape crystals (negative birefringence) and neutrophils

Psuedogout (chondrocalcinosis)

- Calcium pyrophosphate crystal deposition
  - Deposit in articular cartilage
- Joint pain with inflammation (slightly swollen, warm to touch)
  - Usually knee
- Association with hemochromatosis
- Joint aspirate- crystals (positive birefringence)
- Alteration in enzymes-hat produce and degrade pyrophosphate, leading to accumulation

Osteoarthritis (degenerative joint dis.)

- Progressive degeneration of articular cart. and new bone formation
  - Age dependent – universal after 65 (10x more common in women)
  - Weight bearing joints (hip, knee) and hands (PIP and DIP joints)
  - Abnormal load on a weight bearing joint is important predisposing factor
- Articular surface shows erosions, cleft formation
  - Clefts penetrate into underlying subchondral bone leads to (→) surface “fibrillation”
  - Subchondral bone cysts develop beneath articular surface
  - Bone-on-bone friction → dense, sclerotic bone – resembles ivory (eburnation)
Osteoarthritis (degenerative joint dis.)
- Causes reactive bone formation at margins of joints
  - → bony spurs (aka osteophytes)
  - Heberden's nodes – osteophytes at the DIP joints of the finger
  - Bouchard's nodes – osteophytes at the PIP joints of the finger
  - Vertebral body "lipping"
  - "joint mice" – fractured osteophytes and separated cartilage floating in the synovial fluid
- Primary osteoarthritis
  - Cause unknown - ?combo of genetics and mechanical/inflammatory mechanisms
- Secondary osteoarthritis - Congenital hip dislocation, trauma, obesity, hemochromatosis

Osteoarthritis (degenerative joint dis.)
- Clinical manifestations
  - Non-inflammatory joint disease
  - Pain w/passive motion of joint
  - Secondary synovitis
  - Joint stiffness/enlargement
  - Narrow joint space
  - No joint fusion

Nodules
<table>
<thead>
<tr>
<th>Rheumatoid Arthritis</th>
<th>Gout</th>
<th>Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid nodules</td>
<td>Tophus, tophi</td>
<td>Heberden's nodes (women)</td>
</tr>
<tr>
<td>Lesions found in skin overlying pressure points</td>
<td>Articular cartilage of joints and periarticular ligaments; also occur in tendons, soft tissues, ear lobes</td>
<td>Distal interphalangeal joints</td>
</tr>
<tr>
<td>Non-tender, nodules in subcutaneous tissue; central zone of fibrinoid necrosis; rim of glistening epithelial histiocytes, lymphocytes and plasma cells</td>
<td>Large, firm nodules most commonly found adjacent to involved joints; superficial tophi can be associated with ulceration of overlying skin</td>
<td>Justa-articular osteophytes</td>
</tr>
<tr>
<td>Deposition of immune complexes, probably involving rheumatoid factor</td>
<td>Large aggregates of urate crystals surrounded by macrophages, lymphocytes, and foreign body giant cells</td>
<td>Bony outgrowths</td>
</tr>
</tbody>
</table>

HLA Associations
| Systemic Lupus Erythematosus | DR3/DR2
| Rheumatoid Arthritis | DR4
| Multiple Sclerosis | B7 and DR2
| Chronic active hepatitis, Primary Sjogren syndrome | DR3
| Type 1 Diabetes | DR3/4
| Ankylosing Spondylitis, Postgonococcal arthritis | B27

Systemic Lupus Erythematosus
- Young woman, malar rash, photosensitivity
- Connective tissue disease mainly affecting blood, joints, skin and kidneys. Generally occurs as the result of polyclonal B cell activation or medications.
  - Antibodies to RBCs, platelets, WBCs - Hemolytic anemia, thrombocytopenia
  - Immune complex deposition/ decreased complement
  - Polyclonal gammopathy - False positive test for syphilis (VDRL)
- Type II and Type III mechanisms
  - Antibody-mediated destruction of cells
  - Immune complex deposition: renal, joints, serosal linings
- Death from renal failure or infection

Systemic Lupus Erythematosus
- Clinical findings:
  - Autoimmune hemolytic anemia, thrombocytopenia, leukopenia
  - Lympathic: geared up lympahadenopathy and splenomegaly
  - Musculoskeletal: sm. joint arthritis (hands/fingers). No joint deformity
  - Skin:
    - Malar rash- butterfly rash across the cheeks/nose which worsens with sunlight
    - Discoid rash - round scaling plaque often on face which can cause scarring
  - Renal: Causes a diffuse proliferative glomerulonephritis
  - Cardiovascular: fibinosus pericarditis, pericardial effusions, Libmens -Sacks endocarditis (sterile mitral valve vegetation)
  - Respiratory: Interstitial fibrosis of the lungs, pleural effusions
Systemic Lupus Erythematosus

- Laboratory Findings:
  - Positive serum **antinuclear antibodies (ANA)** is present in almost all cases and is highly specific for the disease but not very sensitive
  - **Anti-dsDNA antibodies** can be present; indicate a poor prognosis
  - **Antiphospholipid Antibodies** (lupus anticoagulant) damage vessel endothelium and produce vessel thrombosis which can lead to strokes and spontaneous abortions
  - Anticardiolipin antibodies can produce false pos. on VDRL tests
  - Decreased serum complement (all used up)
  - Immune complex deposition in a band like deposition at the dermal-epidermal junction
  - Can be induced by drugs (Procanamide, hydralazine) but will have Antihistone Ab's and will disappear when the drug is discontinued.

Scleroderma/Sjogren’s Disease

- **Sjogren’s Disease**
  - Middle aged women
  - “sicca syndrome:” dry eyes and mouth, corneal scarring, perforation of nasal septum, fissuring of tongue
  - Immune-mediated destruction of lacrimal and salivary glands
  - Associated w/ non-Hodgkin’s lymphoma
  - Antibodies to SS-A and SS-B
  - Biopsy shows lymphocytic and plasma cell infiltration in minor salivary glands

- **Scleroderma**
  - Older women
  - Dysphagia, sclerodactyly, taut skin on face
  - CREST syndrome: calcinosis, Raynaud’s, esophageal dysmotility, sclerodactyly, telangiectasia; **anti-centromere** antibody
  - Renal onionskinning arteriolosclerosis; fibrosis of lungs (restrictive)
  - Tissue fibrosis mediated by TGF-β

Dermatomyositis, Polymyositis

- **Dermatomyositis**
  - Diffuse pain, decreased proximal muscle strength
  - Violaceous heliotrope rash (esp. peri orbital)
  - Shawl distribution rash; Gottron’s lesions; abnormal nailbed capillaries
  - Destruction of muscle capillaries (vasculitis) results in loss of muscle fibers
  - Increased risk of visceral cancers

- **Polymyositis**
  - Middle-aged woman
  - Symmetrical proximal muscle weakness
  - No skin involvement; no evidence of vascular injury
  - Skeletal muscle shows infiltration of lymphocytes (CD8+ T cells) along with degeneration and regeneration of muscle fibers; direct attack on myocytes
  - Myocarditis, pneumonitis
  - No increased risk of cancer

<table>
<thead>
<tr>
<th>Disease association</th>
<th>Immunofluorescence pattern</th>
<th>ANA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus</td>
<td>Diffuse homogeneous RIm pattern</td>
<td>Anti-ds-DNA</td>
</tr>
<tr>
<td>Drug-induced lupus</td>
<td>Diffuse pattern</td>
<td>Anti-histone</td>
</tr>
<tr>
<td>Sjogren’s</td>
<td>Nucleolar pattern</td>
<td>Anti-SS-A (Ro)</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Diffuse: anti-Scl-70 CREST: anti-centromere</td>
<td>Anti-Jo-1</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Anti-Jo-1</td>
<td></td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Anti-Jo-1</td>
<td></td>
</tr>
<tr>
<td>Mixed connective tissue</td>
<td>Anti-nRNP (U1-ribonucleoprotein)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Speckled pattern Æ non-DNA nuclear constituents (Sm, nRNP; SS-A, SS-B)
**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, macro, 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

- **Kawasaki’s Syndrome** affects children <4yo
  - Disease of young children (most <4 years); Epidemic in Japan, Hawaii
  - Acute segmental necrosis with pronounced inflammation and necrosis resembling PAN
  - Vasculitis of large & medium arteries, esp. coronary arteries
  - Infectious process leading to anti-endothelial cell antibodies; genetic pre-disposition
  - Lymphocyte/PMN infiltrate with necrosis, thrombosis
  - Fever, skin rash (erythema of palms and soles, rash with desquamation), cervical adenopathy, oral/conjunctival erythema ("strawberry tongue") (mucocutaneous lymph node syndrome)
  - TX: IV IgG & Aspirin

- **Buerger’s Disease** affects heavy smokers <age 35
  - Idiopathic segmental thromosing vasculitis of small & medium peripheral arteries = “thromboangiitis obliterans”
  - Involves tibial and radial arteries
  - Intermittent claudication, superficial nodular phlebitis, cold sensitivity, autoamputation of digits

### Churg-Strauss

- **Churg-Strauss**
  - Small vessels : skin, lung, heart
  - Eosinophil-rich granulomatous reaction
  - Affects atopic people
    - Associated with allergic rhinitis, asthma and blood eosinophilia
    - P-ANCA in 70%
  - Coronary arteritis and myocarditis
    - Most common cause of morbidity and mortality
    - Pulmonary necrotizing vasculitis

- **Henoch Schonlein Purpura:** affects children
  - Segmental fibrinoid necrosis with IgA deposition
  - Sequela to upper respiratory infection (maybe post-strep)
  - Palpable purpura, arthralgia, abdominal pain w/ intestinal hemorrhage, renal damage, fever

### Other

- **Buerger’s Disease** affects heavy smokers <age 35
  - Idiopathic segmental thromosing vasculitis of small & medium peripheral arteries = “thromboangiitis obliterans”
  - Involves tibial and radial arteries
  - Intermittent claudication, superficial nodular phlebitis, cold sensitivity, autoamputation of digits

- **Raynaud’s disease** - Not associated with organic lesions
  - **Raynaud’s phenomenon** - Vascular insufficiency secondary to thromboangiitis obliterans, SLE, and systemic sclerosis

### Atherosclerosis

#### Pathogenesis

- Local cell injury → accumulation and oxidation of lipid (LDLs) → endothelial cell activation & increased vascular permeability → adhesion/influx of platelets & monocytes into intima → secretion of cytokines → further influx of inflammatory cells → migration/activation of smooth muscle cells & fibroblasts → secretion of collagen & ECM components

- Oxidized lipid appears to play a central role – they are chemotactic for monocytes, T inflammatory cytokines, macrophage motility and are toxic to endothelial cells/smooth muscle

- **Fatty streaks** (earliest lesions) contain foam cells with variable amounts of proteoglycans, extracellular lipid and T cells – can be seen in toddlers

- Lesions progress with age → become raised → coalesce into plaques

- Over time, fibrotic plaque becomes unstable → “fracture” → exposure of collagen promotes platelet adhesion and local thrombus formation

- Fissuring or rupture of a plaque can produce emboli and acute infarctions at distant sites (e.g MI)

- Lipid/cholesterol emboli a particular problem in the kidney
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

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 arteries
- 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

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

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.

Syphilitic Heart/Aortic Dz

- Luetic aneurysms → assoc. w/ tertiary syphilis
- Confined to thoracic aorta: *usually aortic arch*
  - Involves aortic root can cause aortic insufficiency (AI)
  - “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 - 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

- 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, postero medial 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 Ca\(^{2+}\) 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 pseudomonas)
  – 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

• 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
  – Abscess; hemochromatosis

• 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-atral 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>Vire pericarditis: Non-infectious inflammation; Rheumatic fever, lupus, scleroderma, tumors, uremia</td>
</tr>
<tr>
<td>Fibrinous or Serofibrous</td>
<td>Serous fluid mixed with fibrinous exudate in pericardial fluid that really organizes</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>Purulent or Suppurative</td>
<td>Sensory exudate</td>
<td>Direct extension, bacteremia, lymphatic extension, direct introduction during cardiovascular procedures</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>Blood mixed with fibrinous or suppurative exudate</td>
<td>Immunosuppression potentiates all pathways</td>
</tr>
<tr>
<td>Caseous</td>
<td>Caseation</td>
<td>Tuberculization, direct necrotic involvement of the pericardial space, fistulae, erosion, or bleeding disorder</td>
</tr>
</tbody>
</table>
### Infectious Myocarditis

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<tr>
<th>Condition</th>
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral myocarditis: Coxsackie A, B</td>
<td>Interstitial mononuclear (lymphocytic) infiltration</td>
<td>Most common cause of myocarditis; assoc. with infants, immunosuppressed, pregnant women</td>
</tr>
<tr>
<td>HIV</td>
<td>Focal necrosis of myocytes</td>
<td>Usually follows primary viral infection elsewhere</td>
</tr>
<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: Chagas’ Disease (Trypanosoma cruzi)</td>
<td>Parasitism of myocytes with scattered inflammatory infiltrate</td>
<td>Protozoal South American myocarditis; may affect 50%; most develop progressive cardiac insufficiency due to chronic immune-mediated damage; die 20 yrs. later</td>
</tr>
<tr>
<td>Trichinella</td>
<td>Encapsulated Trichinella with inflammatory infiltrate, eosinophilia</td>
<td>Most common helminthic disease with cardiac involvement</td>
</tr>
<tr>
<td>Bacterial diseases: Corynebacterium diptheriae</td>
<td>Patchy myocyte necrosis with sparse lymphocyte infiltrate</td>
<td>Mediated by diptheria exotoxin</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Spirochete infection of myocytes</td>
<td>Occurs in 2/3</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>Foci of myocardial necrosis with contraction bands; mononuclear infiltrate Similar to reperfusion injury</td>
<td>Seen with pheochromocytomas; large doses of vasopressor agents such as dopamine; cocaine Direct toxicity due to calcium overload and vasomotor constriction of myocardial circulation</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 (transudate)
  - 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 arteriolesclerosis and even atherosclerosis
- Clinical associations
  - Cyanotic heart disease
  - Longstanding 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-shape 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 w/ family history of atopy
- type I hypersensitivity to environmental allergen – IgE mediated

**Intrinsic Asthma (Non-atopic/non-immune)**
- associated w/ aspirin, pulmonary viral infections, cold, exercise, stress

**Acute phase (minutes to hours)**
- mast cell degranulation

**Late phase (hours to days)**
- Eosinophils, basophils, neutrophils
- edema & infiltrates exacerbate luminal narrowing
- Damage to tissue by enzymes/cytokines (eosinophil major basic protein)

### 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

**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 \( \alpha-1 \)-antitrypsin

### Obstructive Pulmonary – Chronic Bronchitis

**Clinical:**
- Asymptomatic until late in the disease
- Prolonging/slowing of forced expiration
- \( \hat{\text{FEV}}_1 \), \( \hat{\text{FVC}} \), \( \hat{\text{FEV}}_1/\text{FVC} < 0.7 \), \( \hat{\text{TLC}} \)
- Barrel chest (\( \uparrow \) A-P diameter)
- Normal \( \text{O}_2 \), \( \uparrow \text{CO}_2 \)
- Weight loss (\( \uparrow \) caloric expenditure for respiration)
- "Peripheral \( \hat{\text{O}}_2 \)" chemoreceptors drive respirations due to chronic high \( \text{CO}_2 \). \( \hat{\text{O}}_2 \) administration may inhibit respiratory drive and lead to respiratory arrest!
- "Pink Puffer"

**Morphology:**
- Hyperinflation of lungs
- smooth muscle hypertrophy
- thickened basement membranes
- goblet cell hyperplasia
- mucus plugs w/ 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)

**Diagnosis:** persistent cough + sputum for at least 3 months in at least 2 consecutive years, associated w/ smoking & pollution

**Submucosal gland hypertrophy \( \Rightarrow \) increase in Reid index**
- Reid index = gland depth/total thickness of bronchial wall
- >50% in chronic bronchitis

**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/out fibrosis
  – due to imbalance between proteases (mainly elastase) & anti-proteases (mainly α1-antitrypsin) in the lungs
• Loss of elastic recoil → 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 α1-antitrypsin activity
  – increased elastase activity results in loss of structure & recoil
• Panacinar – involves the entire acinus of the lower lobes
  – associated w/ α1-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 ↓ (decreased CO diffusion capacity/lung volume/compliance)
• FEV1/FVC = ↑ (>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 → 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)
• 2nd 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 w/ 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 within giant cells – asteroid bodies
- Bilateral hilar adenopathy
- Insidious onset of dyspnea, SoB, hemoptysis
- Dx by exclusion
  - ↓ in CD4 T Helper cells because 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 cardiac 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

• Interstitial: “atypical”, diffuse patchy, more then one love
  – Mycoplasma pneumoniasiae- 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), Chlymidia trachomatis (newborns).

Pneumonia- Causes
• Nosocomial
  – Presents: patients with severe underlying disease, antibiotic therapy, immunosupression, respirators
  – Diagnose: culture
  – Pseudomonas is MC (from respirators)
• Immuno-compromised
  – Presents: Complication of AIDS and bone marrow transplant
  – Pneumocystis is MC (TMP-SMX for prophylaxis and treatment).
  – Others: CMV, Aspirillus

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
  – Cavitary 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-peripheral neoplasm mimicking pneumoniae
    - 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

- **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 cavitary (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

Bronchioalveolar Carcinoma
- Not associated with smoking
- Adenocarcinoma that lines alveolar walls
  - Malignancy of tall type II pneumocytes
- Gross: translucent gray or gray-white areas
- Cells are columnar-to-cuboidal, can project into the alveolar spaces creating papillary-like lesions
- chest X-ray: multiple densities
  - Ill-defined mass/opacity involves distal airways (seen at periphery of lung)
- Symptoms include cough, hemoptysis, and dyspnea
  - May mimic pneumonia

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 fibrous 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 nonsuppurative
    - 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**
  - Otosclerosis- bone deposition along stapes foot plate; conductive hearing loss in young adults
  - Meniere’s Disease – vertigo, nystagmus, nausea, tinnitus, hearing loss; hydromalic dilatation of endolymphatic 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, sinustfect. Bc defective cilia
  - Wegener’s granulomatous: acute necrotizing granulomas; involve lung; c-ANCA

### Nose/Sinuses

- **Neoplasms:**
  - **BENIGN**
    - juvenile angiofibroma (non-metastasizing, hemorrhagic)
  - **MALIGNANT:**
    - nasopharyngeal carcinoma (EBV-associ, children in Africa/China, poor prognosis)
    - pyothoid carcinoma (T-cell lymphoma; necrotizing/ulcer)
    - plasmacytoma (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)
  - Preceeded 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

**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.

**Pseudomembranous form or “thrush”** → superficial, white/grey, inflammatory membrane with organisms enmeshed in a fibrinosuppurative exudate that is scraped of easily revealing an erythematous base.

### Salivary Gland Tumors

**Warthin Tumor (Papillary Cystadenoma Lymphomatosum)**
- Benign, parotid glands only
- M>F, 10% multifocal, 10% bilateral; smoking increases risk
- Round, encapsulated, cystic spaces with mucous/serous fluid, spaces lined by double layer of epithelial cells resting on a dense lymphoid stroma (distinctive oncocytic appearance)

**Mucoepidermoid Carcinoma**
- Minor salivary glands
- Malignant, mixture of squamous + mucous secreting + intermediate cells
- Often infiltrative at margins, mucous containing cysts, divided into low/intermediate/high grade

**Others**
- Adenoid Cystic Carcinoma, Acinic Cell Tumor

### 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, B6 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
  - RBC central pallor on light microscopy = hypochromic, microcytic
  - symptoms: koilonychia, pallor, pale conjunctiva
- (iron is sequestered away from blood to keep it away from blood pathogens, but there is plenty of iron in the body)

### 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: hypocellular 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 tract), 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
- Phenyltoin inhibits the absorption of folate in the jejunum by blocking intestinal conjugase and can also cause 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
- Acute blood loss may show a normocytic anemia as well. However, the reticulocyte index will be increased

### 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)
- Intrinsic factor secreted by parietal cells → peptic digesting and binding to cobalophilins → B12 release from cobalophilins in duodenum → IF-B12 complex absorbed in ileum by binding to IF-specific receptors
  - Pernicious Anemia: Antibodies to gastric mucosa, Antibodies that block IF-B12 complex formation, or Antibodies that block IF-B12 binding and absorption
  - Pancreatic enzymes needed to release B12 from 'rapid binders (cobalophilins)'

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 predominat 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 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

- Pathology:
  - Iron-laden mitochondria assume a perinuclear distribution creating sideroblastic rings within the marrow—Sideroblasts
  - Peripheral smear shows microcytic hypochromic RBCs with some siderotic granules
  - Iron is available but is not properly utilized resulting in hyperferremia and nearly total transferrin saturation in a patient with hypochromic anemia (TIBC is normal to low)
  - Anisocytosis (variable size) and Poikilocytosis (abnormal shape) may be present
  - Basophilic stippling (aggregation of ribosomal RNA) and Pappenheimer bodies (inclusion of phosphocytoglobin iron) are present

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 an 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 cauased 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: Asymtomatic/Silent
  - --/a: More Common in Africa-microcytic anemia
  - --/a: More Common in Asia-microcytic anemia
  - --/--: 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 alpha-microglobulin chain genes on chromosome 16.
- Results in the pathologic formation of Beta-microglobulin tetratmers 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) → microcytic anemia
  - Chronic iron deficient anemia, Thalassemias, anemia of chronic disease, sideroblastic anemia
  - MCH (27-32) → iron deficiency anemia → hypochromia
  - 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

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**Hematology Clinical Pathology**

- Increased red cell distribution width (RDW)
  - 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.

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**Clinical Pathology – Hematology**

- **Lab values and anemia**
  - Fe def, chronic disease, hemochrom, pregnancy
  - Serum Fe ↓ ↓ ↓ N ↑
  - TIBC ↑ ↓ ↑ ↑
  - Ferritin ↓ ↑ N ↑

- Thalassemias will have normal Iron Studies

- Hemoglobin Processing in Intravascular Hemolysis
  - RBC lysis → Hb binds to haptoglobin and taken up by RES cells → depletion of haptoglobin → free Hb oxidized to MetHb → kidney excretion → Prox. Tubule cells take up hemosiderin and slough off

- Leads to hemosiderinuria, methemoglobinemia, hemoglobinuria, hemoglobinemia, increased retic count

- **Clinical Pathology – Hematology**

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

- **Additional Studies** → osmotic fragility test (spherocytes), Hba2 and Hbf levels (thalassemias), Serum B12 and serum folate, serum lead, Hbs (sickle cell)

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**Clinical Pathology – Hematology**

- **Myeloproliferative Disorders – PolycythemiaVera**
  - 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.

- **Polycythemia (COPO, high altitudes)**
  - Differsiates it from 2° polycythemia

- **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 H2O2 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
    - Anykrin mutation leads to decrease in spectrin
- Presents
  - Extravascular hemolysis: splenomegaly, jaundice
  - Increased permeability of spherocytes to Na (diagnostic) (osmostic 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: hemarthrosis, 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

### 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)
- **DIC**: 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

### Essential Thrombocytosis

- 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.

### 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.

### Waldenstrom's Macroglobulinemia

- Syndrome in which a lymphoplasmocytic 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

### 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 for diagnosis)
- symptoms due to anemia, leukopenia, thrombocytopenia
- myeloblasts contain myeloperoxidase-positive granules & AUER RODS. TdT (terminal deoxytransferase) is negative
- AML is classified (M0-M7) based on marrow morphology and chromosomal aberrations…t(8;21) or t(15;17) for example
- variable WBC counts

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) → 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 → 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, hairlike cytoplasmic projections
• Clinical findings:
  – ↑ Tartrate resistant acid phosphatase (TRAP)
  – Splenomagaly → dragging sensation
  – Pancytopenia from marrow failure → 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>
</tr>
</thead>
<tbody>
<tr>
<td>CLL/Small cell lymphoma</td>
<td>Small, mature looking lymphocytes</td>
<td>Diffuse effacement of lymph node, proliferation centers, leukemia/smudge cells</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>Small cells with cleaved nuclei</td>
<td>Nodular or nodular and diffuse growth, prominent white pulp follicles in spleen</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>Large cell size</td>
<td>Diffuse growth</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia/lymphoma (B-cell)</td>
<td>Lymphoblasts</td>
<td>Bone marrow – mostly leukemic presentation, high mitotic rate</td>
</tr>
<tr>
<td>Acute lymphoblastic (T-cell)</td>
<td>Lymphoblasts</td>
<td>Thymic involvement, high mitotic rate</td>
</tr>
</tbody>
</table>

Small Cell Lymphocytic/CLL
• (associated w/ chronic leukemia → 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 (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

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

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**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**

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**Lymphocyte Predominant Hodgkin’s Disease**

- 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**
Pathology Review Flash Cards
GI, Liver
Spring 2009

Esophagus Fistulas and Stenosis
• Tracheoesophageal Fistulas
  – upper esophagus ends in a blind pouch (atresia),
    lower esophagus connects to trachea near bifurcation
    • this is the most common variant (90%)
  – fistula may connect to upper blind pouch (2nd most
    common)
  – Atresia is associated with congenital heart disease
    and OTHER GI malformations – polyhydramnios in
    the fetus (can’t swallow amniotic fluid)
• Stenosis-inflamatory, submucosal thickening
  with atrophy of the muscularis propria
  – causes-radiation, reflux, scleroderma, caustic injury

Esophagus Diverticula
• Zenker’s-above UES
  – assoc. w/ cricopharyngeus motor dysfunction
  – presents with regurgitation w/out dysphagia
  – Can complicate with aspiration → pneumonia
• Traction-middle of esophagus
  – thought to be due to congenital motor dysfunction
  – usually asymptomatic
• Epiphrenic-above LES
  – due to failure of LES to relax upon swallowing
  – presents with nocturnal regurgitation of fluid

Esophagus Abnormalities
• Achalasia-lack of peristalsis, failure of relaxation and
  increased resting tone of LES
  – Esophagus will be dilated above LES, myenteric plexus will
    be absent
  – Seen secondarily to Chagas disease from T. cruzi infection
    – predisposed to sq. cell carcinoma of esophagus (5%)
• Sliding hiatal hernia-protrusion of cardia thru diaphragm
  – results in bell shaped dilatation above diaphragm
  – Paraesophageal hiatal hernia- greater curvature protrusion
    – esophagus is not dilated
    – symptoms-heartburn, reflux; complications-ulceration and
      perforation

Esophageal Varices
• Esophageal varices
  – Collaterals form around lower esophagus and
    proximal stomach in the esophageal mucosa and
    submucosa secondary to portal HTN
  – Varices are tortuous vessels with increased
    intravenous pressure
  – seen in 90% of cirrhotic patients; assoc. w/ alcohol
    (US) and schistosomiasis (worldwide)
  – rupture results in massive hemorrhage (50% mortality)

Mallory Weiss Tears
• longitudinal tearing of esophagus following
  severe retching
• usually occurs at gastro-esophageal
  junction or proximal gastric mucosa
• Seen in alcoholics and bulimia
• Bleeding usually not severe and self-limited
Infectious Esophagitis
- Associated with immunosuppression HIV/AIDS
- Candida
  - Patched or diffuse involvement of mucosa
  - Gray-white pseudomembranes
- Herpes
  - Punched-out ulcers
  - Intranuclear inclusions seen in degenerating epithelial cells
- CMV
  - Punched-out ulcers
  - Intranuclear and cytoplasmic inclusions found in papillary endothelium and stromal cells at the base of the ulcer

Reflux Esophagitis
- Most common cause of esophagitis; adults >40
  - assoc. w/ alcohol, tobacco, decreased LES tone, hiatal hernia, pregnancy, scleroderma
- 3 characteristic features:
  1. inflammatory infiltrate- neutrophils, eosinophils, lymphocytes
  2. basal zone hyperplasia
  3. Elongation of lamina propria papille
- Presents w/ dysphagia, heartburn, regurgitation, hematemesis, or melena
- Complications: bleeding, stricture development, Barrett’s esophagus

Barrett’s Esophagus
- Complication of long-standing esophagitis
- Metaplasia of the distal esophagus → squamous mucosa changed to columnar epithelium with intestinal goblet cells
- Metaplasia seen as red, velvet mucosa against a background of smooth, pale, squamous cell mucosa
- Begins near squamocolumnar junction and goes upward
- Associated with increased risk of adenocarcinoma in the bottom 1/3 of the esophagus

Esophageal Neoplasms
- Squamous cell carcinoma
  - 90% of esophageal CA worldwide- 50% in US
  - Assoc. w/ alcohol, tobacco, and nutritional deficiencies
  - Distribution: 20% upper, 50% middle, 30% lower
  - Begin as small, gray-white plaque areas but can become protruded, flat, or excavated and are often large at Dx
- Adenocarcinoma:
  - Distal 1/3 of esophagus- assoc. w/ Barrett’s esophagus
  - Mucin-producing glandular tumors with intestinal-type features
- Both present with dysphagia, weight loss, hematemesis
- Both spread by direct extension to adjacent structures

Stomach – Congenital Lesions
- Gastric Heterotopia:
  - patches of ectopic gastric mucosa in duodenum or more distal sites
  - causes bleeding and ulcerations (esp. w/Meckel’s diverticulum)
- Diaphragmatic Hernia:
  - weakness or partial-to-total absence usually on the left
  - herniation of abdominal contents in utero
  - results in respiratory insufficiency
- Pyloric Stenosis:
  - familial; 1/300-900 live births; 3-4x more common in boys
  - projectile vomiting in second or third week of life
  - palpable mass on exam
  - Results from hypertrophy/hyperplasia of pyloric muscularis propria

Helicobacter Pylori Infection
- Most important cause of chronic gastritis
  - 90% of pts. w/chronic gastritis of the antrum
- Colonizes 50% of persons over age 50, most of which are asymptomatic
- Gram negative rod with flagella
  - elaborates urease to produce ammonia and buffer gastric acid
- Reside in superficial mucous layer among microvilli
  - they do not invade the mucosa
- May predispose to gastric carcinoma and lymphoma
Autoimmune Gastritis (Pernicious Anemia)
- Accounts for <10% of chronic gastritis
- Autoantibodies to gastric gland parietal cells and intrinsic factor
  - Results in gland destruction and mucosal atrophy
- Associated with other autoimmune diseases
  - Hashimoto’s and Addison’s
- Autosomal dominant familial occurrence well-established
- Long-term risk of gastric carcinoma is 2-4%

Acute Gastric Ulceration
- Assoc. w/ NSAID therapy & physiologic stress
- Stress ulcers seen in patients with shock, burns, sepsis, or severe trauma (5-10% of ICU patients)
- Ulcers are circular and small; anywhere in stomach, dark brown base (“cigarette burns”)
- Surrounding mucosa is normal with no scarring or thickening of blood vessels
- Cushings ulcers → due to increased intracranial pressure or post-intracranial surgery
- Curling’s ulcers → located in proximal duodenum

Zollinger-Ellison Syndrome
- Hypersecretion of gastrin from gastrinoma (pancreatic, duodenal, or elsewhere)
- Ulcers present in 90-95%; most commonly found in duodenum but may occur in more distal gut
- >50% metastasized at time of diagnosis
- Ulcers intractable to usual modalities of therapy
- Diarrhea is common presenting symptom
- Treat with H2 blockers and surgical removal of tumor

Stomach – Peptic Ulcer Disease
- Ulcers usually solitary → from chronic mucosal damage 2° to acid and pepsin secretion
- Location: duodenum (1st portion) > stomach (antrum) > gastroesophageal junction (GERD)
- Associated with:
  - H. pylori in 100% of duodenal and 70% of gastric ulcers
  - Chronic NSAID use suppresses prostaglandins
  - Corticosteroids & hypercalcemia also contribute
  - Tobacco impairs mucosal blood flow

Peptic Ulcer Disease cont.
- Gross morphology:
  - Size doesn’t differentiate benign from malignant
  - Punched-out lesion; no heaped-up margins as in malignant lesions; ulcer base is smooth & clean
  - Fibrosis of surrounding wall leads to spoke-like folds
- Microscopic morphology:
  - Non-specific inflammatory infiltrate w/neutrophils
  - Deep-layer granulation tissue w/mononuclear cells
- Clinical:
  - Epigastric gnawing, burning, or aching pain; worse at night and 1-3 hrs. after a meal
  - Nausea & vomiting; pain may be referred to back

Hypertrophy/Hyperplasia
- Menetrier disease
  - Hypersecretion of mucus with no hyperacidity (glandular atrophy)
  - May result in protein-losing gastroenteropathy
  - Infrequently, metaplasia of mucosa associated with increased incidence of gastric carcinoma
- Parallels between stomach and colon
  - Polyps can be hyperplastic or adenomatous
  - Adenomatous polyps associated with foci of carcinoma
  - Hyperplasia with atypia predisposes to cancer
  - In stomach, associated with chronic gastritis
Gastric Polyps

- Any nodule or mass projecting above mucosa; uncommon (0.4%), 3-5% in Japan
- Majority are non-neoplastic (90%) and represent hyperplastic lesions
  - Due to chronic inflammation
  - Seen most commonly with chronic gastritis
- **True adenomas**: 5 to 10% of gastric polyps; have dysplastic epithelium and malignant potential
  - M:F ratio 2:1; up to 40% contain a focus of carcinoma
  - Autoimmune gastritis and colonic polyposis syndromes predispose to gastric adenomas

Gastric Carcinoma

- Represent 90-95% of malignant gastric cancers; others are lymphomas, carcinoids, & stromal tumors
- Most prevalent in Japan (smoked salmon?)
- 5 yr. survival <20%
- ½ are bulky tumors resembling colonic adenocarcinoma
- ½ are diffuse & infiltrative (signet ring cells)
- Contributing factors: H. pylori w/ chronic gastritis, autoimmune gastritis, diet, cigarettes (NOT alcohol)

Malabsorption Syndromes

- **Celiac Sprue** – immune mediated hypersensitivity reaction to gluten/glutamin; proximal small intestine
  - Blunting of villi w/ hyperplastic crypts and diffuse enteritis
  - Lymphocytes in lamina propria; linked to HLA B8; associated with dermatitis herpetiformis
  - Increased risk of malignancy (usually T cell lymphoma)
- **Tropical Sprue** – Caused by overgrowth of enterotoxigenic organisms
  - Affects all levels of small intestine (variable enteritis)
  - Occurs days-weeks after diarrheal disease following trip to endemic area
  - Treat w/ broad spectrum antibiotics

- **Whipple’s Disease**
  - Caused by gram+ actinomyco• T rode • •• s • •• t h e 
  - Affects intestine, CNS and joints
  - Distended macrophages in lamina propria w/ PAS+ granules
  - Villi expansion→"shaggy" appearance
  - NO inflammation; YES lymphadenopathy and hyperpigmentation
- **Disaccharidase (Lactase) Deficiency**
  - No morphological changes
  - Osmotic diarrhea; ↑ H₂ production → abdominal pain/distention, bloating
  - Usually acquired, can be congenital; blacks>whites
- **Abetalipoproteinemia**
  - Autosomal recessive (rare)
  - Deficiency of apoprotein B →unable to assemble chylomicrons and export lipoproteins → store triglycerides in cells w/ lipid vacuolation
  - Circulating acanchoctyes or burl cells
  - Low LDL and VLDL
  - Results in steatorrhea or failure to thrive
- **Bacterial Overgrowth**
  - Associated with luminal stasis, achlorhydria, immune deficiencies
  - Malabsorption due to bacterial use of nutrients, breakdown of bile acids, and mucosal inflammation
Nutritional Aspects of Malabsorption

- Almost all syndromes will cause weight loss, anorexia, abdominal distension, borborygmi, muscle wasting
- General endocrine: amenorrhea, impotence, infertility
- Fat malabsorption causes deficiencies of related vitamins
  - Vitamin A: dermatitis, hyperkeratosis, peripheral neuropathy
  - Vitamin D: hypocalcemia with osteopenia and tetany
  - Vitamin K: abnormal bleeding

- Protein deficiency with retained carbohydrate absorption leads to low albumin with edema, as in pancreatic insufficiency

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Crohn’s Disease

- f>m; mainly western population
- smoking is risk factor
- peaks in 20’s-30’s
- may involved any part of bowel (mouth→anus)
- skip lesions
- lesions coalesce into linear ulcers
- non-caseating granulomas found throughout bowel
- transmural involvement=fissures and fistulas
- string sign=narrowed lumen with thick wall
- 5-6x increase in GI cancer
- more skin and liver extraintestinal effects than UC

Ulcerative colitis

- whites > blacks, found globally
- peaks 20-25 yo
- mucosa and submucosa of rectum and large intestines; lesions in continuous fashion without skip lesions
- involves rectum and extends proximally; rarely any ileum
- Inflammatory pseudopolyps—extensive ulceration and hemorrhage with areas of regeneration; no granulomas
- can have nerve damage leading to toxic megacolon
- Ulcers and crypt abscesses containing neutrophils
- bloody, mucoid diarrhea may last for days-months
- 20-30x incr risk for GI cancer
- Complications include: toxic megacolon, primary sclerosing cholangitis (HLA-B27 positive) and colon adenocarcinoma

Appendicitis

- Fecalith obstructs proximal lumen (50-80%)
- Continued secretion of mucinous fluid causes increased intraluminal pressure
- Collapse of venous drainage results in ischemia
  - Inflammatory edema and exudate result in more ischemia
  - Secondary bacterial proliferation
- Histologic criteria= neutrophilic infiltrate of muscularis
- Presents as RLQ pain, N/V, fever, high WBC
Congenital Intestinal Disease

- Atresia and Stenosis
  - Uncommon, duodenum most common site, colon never involved, can occur from developmental failure/intrauterine vascular accidents/intussusceptions
  - Atresia can be a mucosal diaphragm or a string-like segment of bowel connecting normal pieces
  - Stenosis (more rare) can be either of those but with a partial opening

- Meckel Diverticulum
  - Failure of involution of the vitelline duct, antimesenteric side of bowel w/in 2' of ileocecal valve
  - Contains all three layers of bowel wall
  - Heterotopic rests of tissue often found (gastric, pancreatic)

- Congenital Aganglionic Megacolon (Hirschsprung Disease)
  - Lack of neural crest cell migration/premature death of ganglia (lack of submucosal and myenteric plexus)
  - RET gene may be involved
  - Rectum always involved, more proximal colon is variable
  - Colon proximal to lesion undergoes dilation and hypertrophy, eventual rupture, sterocoral ulcers may be seen

Adhesions/Volvulus/Intestinal Carcinoids

- Adhesions – usually from previous surgery (also endometriosis and radiation); #1 cause of small bowel obstruction.
- Volvulus – cecum in young adults, sigmoid in older; bowel twists around mesenteric root with strangulation and obstruction; Risk factors = chronic constipation, pregnancy, laxative abuse
- Carcinoids – malignant neuroendocrine tumors; bright yellow
  - #1 site is appendix, no mets from appendix; most common site producing liver mets is the terminal ileum.
  - Carcinoid syndrome only seen secondary to liver mets.
    - Flushing, diarrhea, 5-HIAA seen in urine

Smooth Muscle Tumors

- Leiomyoma
  - Benign, often arise in uterus, also in erector pili muscles in skin, nipples, scrotum, and labia
  - Multiple lesions associated w/AD inheritance
  - No larger than 1-2cm, fascicles of spindle cells intersecting at right angles, blunt-ended elongated nuclei with little atypia and mitotic figures

- Leiomyosarcoma
  - Most in skin and deep soft tissues of extremities and retroperitoneum, painless firm masses
  - Malignant spindle cells in interweaving fascicles, may have prominent myxoid stroma or epithelioid cells; >10 mitoses per high power field
  - Stain with antibodies to vimentin, actin, smooth muscle actin, and desmin

Diverticulosis/ Diverticulitis

- Diverticulosis
  - Common in elderly
  - Often multiple; outpouchings of mucosa from: 1) focal weakness in colonic wall and 2) increased intraluminal pressure
  - Most in sigmoid colon alongside taeniae coli
  - Most asymptomatic- some abdominal discomfort, constipation, distension
  - MCC of hematocritia- enlarged vessels often at apex of diverticulum just below the mucosa

- Diverticulitis
  - Presents as “left sided appendicitis”
  - Obstruction or perforation of diverticula → inflammation, pain, bacterial overgrowth
  - Often resolves spontaneously- rarely causes fibrosis or generalized peritonitis

Diverticulosis/ Diverticulitis
### Ischemic Bowel Disease
- Usually ACUTE occlusion of a major supply trunk
- Older individuals, usually with pre-existing abdominal disease (adhesions, torsion)
- Morphologic patterns
  - Transmural infarction = implies mechanical compromise of major mesenteric vessels
  - Appears hemorrhagic due to blood reflow; arterial lesions are well demarcated; venous occlusions fade gradually
  - Within 1 to 4 days, bacteria cause gangrene and perforation
- Mucosal or mural infarction = results from hypoperfusion (either acute or chronic)
  - Epithelial sloughing with ulceration, absence of inflammation
  - Bacterial superinfection may result in pseudomembranous colitis
  - Chronic ischemia has fibrosis that may lead to stricture formation
  - Notoriously segmental and patchy

### Angiodyplasia
- Occurs in elderly (after 6th decade)
- Account for 20% of significant lower intestinal bleeding
- Pathology
  - Ectatic nests of pre-existing veins, venules, and capillaries
  - Tortuous dilatations of mucosal and submucosal vessels of the cecum and right colon
- Pathogenesis
  - Focal dilatation and tortuosity of vessels from intermittent occlusion secondary to normal colonic contraction

### Adhesions/Volvulus/Intestinal Carcinoids
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### Secretory Diarrhea: viral
- **Rotavirus** (11 segments dsRNA, non-enveloped, 2 layer capsid, core with complete transcriptional system)
  - 25-65% diarrhea infants small children (6-24 months), 140 million inf & 1 million deaths/yr
  - Outbreaks in peds units and daycares
  - Path: 10 virions for infection, 2 day incubation → selectively infects and destroys enterocytes (villus cells) in small intestine, doesn’t infect crypt cells → repopulation by secretory cells → massive loss water/electrolytes + osmotic diarrhea due to incomplete absorption → lots of virus shed in stools
  - Antibodies provide partial protection, in mother’s milk (most common time infection is weaning)

- **Caliciviruses = Norwalk** (pos ssRNA, non-enveloped icosahedral, fecal-oral)
  - Non-bacterial food-borne gastroenteritis epidemics in all ages
  - Exposure of individuals to common source
  - 2 day incubation → 12-60 hours nausea, vomiting, diarrhea, cramps

- **Astrovirus** (neg ssRNA, non-enveloped, filamentous and pleomorphic)
  - Children (4% all gastroenteritis)
  - Anorexia, headache, fever with diarrhea

- **Adenovirus** (dsDNA, non-enveloped icosahedral capsid, fiber – attach hemaglutinin, no enzymes in core, released by cell lysis)
  - Enteric serotypes common cause of infant diarrhea
  - 1 week incubation → moderate gastroenteritis with vomit lasts 10 days
  - Atrophy of villus and hyperplasia of crypts (as in Rotavirus) causes loss of fluids/electrolytes and malabsorption

### Secretory Diarrhea: viral
- **Astrovirus** (neg ssRNA, non-enveloped, filamentous and pleomorphic)
  - Children (4% all gastroenteritis)
  - Anorexia, headache, fever with diarrhea
- **Common Morphological Features**
  - Small intestinal mucosa with shortened villi and lymphocytic infiltrate into lamina propria
  - Vacuolization and loss of microvillus brush border
  - Crypts are hypertrophied
### Secretory Diarrhea: enterotoxin mediated

- **Vibrio cholera** (-, comma shaped, alkali tolerant, oxidase positive) fecal-oral, killed by stomach acid so need large innoculation
  - Path: Flagella attach to epi → secrete toxin → activate adenylate cyclase → cAMP formed → secretion of Cl- and bicarb → diarrhea
  - Cholera toxin: 5 B subunit binds ganglioside Gm1, A endocytosed, split A1, A2 → A1 binds ARF → NAD+ARF-A1 ribosylates Gsalpha → activates
  - Morph: proximal intestine, mucus depleted crypts

- **E. coli (ETEC)** (-, rod, oxidase neg, FA... “traveler’s diarrhea”
  - Path: adhere to epi via pili → HL and HS enterotoxins → loss fluids and electrolytes

- **Bacillus cereus** (+, rod, motile, endospore, FA, cat positive)
  - Path: enterotoxins, HL and HS

- **Clostridium perfringens**
  - Path: necrotic enterocolitis (strain C)... enterotoxin superantigen Gastroenteritis (strain A)... food poisoning
  - Morph: similar to V. cholera, but with some epi damage, can be necrotizing

### Dysentery

- **Shigella** (-, FA, non-motile, non-coliform, S. flexneri) fecal-oral, virulent
  - Path: invades epithelia → escapes phagolysosome → lysis cell
  - Shigatoxin causes mucosal necrosis: fibrinosuppurative exudate + hemorrhagic colitis and hemolytic uremic syndrome
  - Sequence: reactive arthritis: Reiter’s syndrome (nongonococcal urethritis+reactive arthritis+conjunctivitis) 80% HLA-B27, one month following genitourinary (Chlamydia) or GI (Shigella, Salmonella, Yersinia, Campylobacter) low back, ankles, knees, feet asymmetrically
  - Morph: hyperemia, edema, enlargement of mucosal lymphoid nodules in distal colon → inflammation and erosion with thick purulent exudate

- **Salmonella** (-, flagellate, non-coliform, produce H2S)
  - Sign: “rose spots” - chest/abdomen, hepatosplenomegaly, dysentery
  - Labs: neutropenia
  - Typhoid fever → Signs: “rose spots” - chest/abdomen, hepatosplenomegaly, dysentery
  - Enteric fever: fever, bacteremia – associated with sickle cell and schistosomiasis
  - Food poisoning: vomiting + diarrhea, self-limited except for immunocompromised
  - Sequence: reactive arthritis (with Shigella, Salmonella, Yersinia) and Guillian Barre Syndrome
  - C. jejuni Path: flagella binds epi → invades mucosa → causing diarrhea, dysentery, or enteric fever (when disseminates to mesenteric nodes with toxin/invasive lesion, crypt abscess)
  - Sequence: reactive arthritis (with Shigella, Salmonella, Yersinia) and Guillian Barre Syndrome
  - C. festus = undercooked beef, grows 25, capsule S protein inhibits C3b binding
  - C. jejuni = chicken, grows 42

- **Campylobacter** (-, comma, flagellate, oxidase and catalase positive) most common cause: diarrhea, gastritis, and dysentery... can develop to sepsis... bad for immunocompromised
  - C. jejuni: Path: flagella binds epi → invades mucosa → causing diarrhea, dysentery, or enteric fever (when disseminates to mesenteric nodes with toxin/invasive lesion, crypt abscess)
  - Sequence: reactive arthritis (with Shigella, Salmonella, Yersinia) and Guillian Barre Syndrome
  - C. festus = undercooked beef, grows 25, capsule S protein inhibits C3b binding
  - C. jejuni = chicken, grows 42

- **Clostridium difficile** (+, anaerobe, normal gut flora, sporulator) antibiotic-induced colitis
  - Path: long course broad spec antibiotics → overgrowth C. difficile → production apoptotic toxins: enterotoxin A and cytotoxin B → inflammatory cells over lesion form pseudomembrane
  - Clinical: acute or chronic diarrhea after surgery or antibiotics
  - Morph: formation of fibropurulent membrane
  - UNIQUE → denuded epithelium with neutrophil infiltrate, fibrin thrombi in lamina propria, and mushrooming mucopurulent exudate from crypts
Dysentery
- *E. coli* (g-, rods, green sheet on EMB, coliform, FA)
- *(O157:H7)* no fermentation sorbitol + grows at 45, commensal in animals, contaminated meat and unpasteurized milk
  - Path: shiga-like toxins acts on receptor (only in humans) \(\rightarrow\) mRNA translation stopped \(\rightarrow\) mucosal invasion \(\rightarrow\) damage cells causing abdominal pain and diarrhea
  - Sequelae: hemolytic uremic syndrome = hemolytic uremia, renal failure, and thrombocytopenia... mostly in young and old
- *(EIEC)* Path: attaches and invades colon \(\rightarrow\) inhibits absorption \(\rightarrow\) initiates inflammation \(\rightarrow\) watery to bloody diarrhea

Non-neoplastic colonic polyps

1. Hyperplastic polyps
   - Most common type of polyp
   - Can occur anywhere in the colon or small intestine
   - Clinically insignificant but may be mistaken for adenomatous polyp

2. Inflammatory polyps (2 types)
   - Benign lymphoid polyps and inflammatory pseudopolyps
   - Consist of granulation tissue and remnants of mucosa
   - Caused by chronic inflammatory bowel disease

Non-neoplastic colonic polyps

3. Hamartomatous polyps (2 types)
   - Juvenile polyps
     - Only located in the rectum
     - Occur mostly in children (can also be seen in adults)
   - Peutz-Jeghers (PJ) Polyps
     - Part of PJ syndrome
     - PJ syndrome = polyps of colon and region, melanotic accumulation in mouth, lips, hands, and genitals
     - PJ polyps have no malignant potential, but PJ syndrome associated w/adenocarcinoma of colon and CA at other sites (stomach, breast, ovary)

Familial Adenomatous Polyposis

- uncommon autosomal dominant disorders
- differs from Peutz-Jeghers syndrome in that polyps are adenomatous, instead of hamartomas
- onset of polyps 2nd-3rd decade, followed by cancer in 10-15 years
- Features
  - innumerable adenomatous polyps that carpet the mucosal surface (500-2500); minimum of 100 polyps necessary for diagnosis
  - frequency of progression to colon adenocarcinoma approaches 100%
  - vast majority of polyps are tubular adenomas
  - cancer prevention includes colectomy and early detection of disease in first-degree relatives

Colon Cancer

- Vast majority are adenocarcinomas; generally arise from pre-existing dysplastic proliferation (adenomatous polyps)
- Predisposing factors include diet (low fiber, high fat, high refined carbohydrates), adenomatous polyps (especially villous), inherited multiple polyposis syndromes (familial polyposis, Gardner syndrome, and Turcot syndrome), long standing ulcerative colitis, and genetics.
- Most people affected are aged 60-70, M>F.
- Lesions are generally slow growing.

Colon Cancer

- Right sided lesions grow as polyps or can fungate and cause fatigue, weakness, and iron deficiency anemia from blood loss.
- Left sided lesions occur as circular lesions around the colon (napkin ring) that cause occult bleeding, changes in bowel movements, and LLQ cramping pain.
Colon Cancer

- The most important prognostic factor is depth of tumor invasion.
- Stage A – limited to mucosa, 100% 5 year survival.
- Stage B – invades muscularis but not lymph nodes, 50% 5 year survival.
- Stage C – spread to local lymph nodes, 25% 5 year survival.
- Spread is by local invasion into lymphatics and the bloodstream; common metastasis to lymph nodes, liver, lungs and bones.

Hepatitis A

- RNA picornavirus
- Transmission: Fecal/oral, liver/bile/stools/blood
- Acute infection only with no carrier state
- May present with jaundice without other symptoms
- Diagnosis
  1) anti-HAV antibodies
  2) high IgM antibodies diagnostic; switches to IgG with convalescence

Hepatitis B

- Double-stranded DNA hepdnavirus, "Dane particle"
- Transmission through all body fluids excluding stool, vertical transmission leads to infant carrier state
- Can develop acute (most cases) or chronic infection - T-cell mediated immunity responsible for disease manifestations
- Long incubation (3 months) with carrier state
- Necessary for Hepatitis D infection

Hepatitis C

- RNA flavivirus- HCV
- Blood borne transmission, post-transfusion hepatitis, post- transplant, not (very rare) sex
- Chronic infection with progression to cirrhosis
- Chronic infection with HCV is associated with the development of hepatocellular carcinoma
- Persistent infection and chronicity hallmarks of HCV
- Similar disease course to HBV
- Dx: anti-HBC antibody (IgM or IgG due to chronicity) and PCR of viral DNA

Hepatitis D & Hepatitis E

- Hepatitis D – delta agent, RNA virus
  - Africa, Middle East, southern Italy
  - Only able to replicate and cause infection when encapsulated by HBsAg
  - Acute coinfection – after exposure to serum containing both
    - HBV must establish first to provide HBsAg – mild to fulminant
  - Superinfection – Chronic HBV carrier with inoculation of HDV
    - 80% develop chronic, progressive dx, leading to cirrhosis
- Hepatitis E – water-borne, enteric transmission
  - Young adults in Asia, India, sub-Saharan Africa, Mexico
  - 6 week incubation, self-limiting disease (2-4 wks)
  - High mortality among pregnant women!
Hepatitis morphology

- Acute Hepatitis: The portal tracts will be infiltrated with a mixture of inflammatory cells
  - ballooning degeneration of the cells. This can progress to rupture of the cell membrane and cytolysis.
  - CD8 T cell induced apoptosis; cells to shrink and become intensely eosinophilic with fragmented nuclei (Councilman Bodies)
  - Severe loss of hepatocytes can lead to bridging necrosis connecting portal and central regions.
  - HBV infected - cytoplasm packed with spheres and tubules of HBsAg; finely granular eosinophilic cytoplasm "ground glass appearance"
- Chronic Hepatitis: smoldering loss of hepatocytes leads to bridging necrosis and fibrosis. This can progress to cirrhosis with fibrous septae surrounding regenerative nodules.

Alcoholic Liver Disease- Fatty Liver

- Steatosis(Fatty Change/Perivenular Fibrosis)
  - Liver is grossly enlarged, soft, yellow and greasy
  - Accumulation of small (microvesicular) lipid droplets in hepatocytes which become macrovesicular deposits with chronic intake
  - excess NADH shunts towards fat synthesis
  - impaired assembly and secretion of lipoproteins
  - hepatomegaly with mild increase in bilirubin and alkaline phosphatase levels
  - With long standing disease, fibrosis occurs around central vein where damage become irreverible
- Fatty liver changes are completely reversible

Alcoholic Liver Disease- Hepatitis

- necrosis, inflammation, fibrosis, Mallory bodies
- Occurs after a binge- causes P450 induction and high acetaldehyde levels, both of which result in oxidative damage to membranes.
- malaise, anorexia, tender hepatomegaly
- high bilirubin and alkaline phosphatase
- may be reversible
- Fibrosis- sinusoidal and perivenular fibrosis
- Neutrophil reaction- accumulation around degenerating cells; also monocytic and lymphocytic infiltrates

Alcoholic Liver Disease- Cirrhosis

- As necrotic tissue is lost, liver becomes shrunken and is replaced by fibrotic tissue
- Typical pattern: micronodular cirrhosis
  - nodule formation separated by fibrous tracts surrounding regenerating hepatocytes
  - Form of postnecrotic cirrhosis
- May occur with or without previous steatosis or hepatitis.
  - chronic necrosis and inflammation leads to loss of liver tissue, nodular fibrosis, and portal hypertension.
  - elevated bilirubin, aminotransferase and low proteins (albumin, clotting factors)
- causes: variceal hemorrhage, ascites, caput medusa, malaise, hepatocellular carcinoma

Fetal Alcohol Syndrome

- Alcohol abuse during pregnancy
  - 1200 cases per year
- Growth retardation, microcephaly, facial dysmorphism, congenital anomalies
  - Fetal neurological tissue particularly susceptible to damage from alcohol
- Most common cause of preventable mental retardation in the US

Hemochromatosis - General

- Lifelong iron overload
  - lack of negative feedback regulation of iron absorption with accumulation of 0.5-1.0g/year
  - Symptoms in 5th-6th decade with 50g accumulation (nl. 1-2g)
- Genetic susceptibility is autosomal recessive
  - Linked to HLA-H on chromosome 6
  - 2nd forms from repeated transfusions or excess iron intake
- Male:Female ratio 7:1
  - Women protected by physiological iron loss (menstruation)
- Classic triad: micronodular cirrhosis, brittle diabetes, skin hyperpigmentation
  - Hepatocellular carcinoma risk increased 200-fold
Hemochromatosis - Pathology
- Deposition of ferritin and hemosiderin in organs
  - Free radicals form in Fenton reaction
  - Lipid peroxidation, stimulation of collagen formation, and DNA damage
- Hepatic hemosiderosis with micronodular cirrhosis
- Pancreatic iron deposition with fibrosis
- Myocardial iron deposition
  - arrhythmia, restrictive cardiomyopathy
- Iron deposition in many other organs
  - excess melanin production, arthralgia, hypogonadism, impotence

Wilson's Disease (hepatolenticular degeneration)
- Autosomal recessive deficiency in hepatic canalicular copper transport protein
  - Liver cannot excrete copper in bile or load onto ceruloplasmin
  - First accumulates in liver, then spills into blood by age 5 and deposits in organs
  - Levels typically symptomatic in young adulthood (rarely younger than 5 or older than 30)
- Deposits in liver with fatty change and chronic hepatitis with Mallory bodies
  - mixed cirrhosis and hepatic encephalopathy
- Copper deposits in brain, especially basal ganglia
  - Parkinsonism, inappropriate behavior, and dementia
- Kidney disease leading to osteoporosis, renal calculi
- Kayser-Fleischer rings: copper deposits outside iris

α-1 Antitrypsin Deficiency
- Autosomal recessive mutation of protease inhibitor synthesized in hepatocytes
  - Does not migrate to Golgi apparatus and precipitates in endoplasmic reticulum; 10% of homozygotes show liver dis.
  - Chronic hepatitis in childhood with micronodular cirrhosis or latent disease presenting in adulthood with macronodular cirrhosis
  - Can cause neonatal cholestasis and biliary tract fibrosis
  - PAS-positive, diastase resistant globular cytoplasmic inclusions
  - Infrequently fatty change and Mallory bodies
- 2-3% lifetime hepatocellular carcinoma risk

Reye's Syndrome
- Rare, often fatal childhood illness (6 months-15 years)
  - Widespread mitochondrial injury with encephalopathy and liver injury
  - Pathogenesis unclear, but associated with viral infections (esp. influenza, chicken pox) treated with aspirin
  - Usually begins 3-7 days after viral illness presents
- Sudden onset of vomiting and lethargy with progressive rostral-caudal degeneration
  - Microvesicular fatty liver
  - Anion-gap acidosis, hyperammonemia, hypoglycemia, elevated free fatty acids, hyperbilirubinemia, elevated liver enzymes
  - Cerebral edema and swelling of astrocytes
  - 25% progress to coma; 10-40% fatal

Pharmaceutical Liver Toxicity
- Direct toxicity of metabolites to hepatocytes, immune-mediated, or hormonal injury
- Cholestasis—hyperbilirubinemia with pattern indicative of biliary obstruction
- Hepatocyte injury
  - Mild toxicity causes fatty liver change
  - Severe injury can result in fulminant necrosis
- Idiosyncratic reaction—risk does not change with dose
  - Cholestasis: typical antipsychotics
  - Hepatocellular injury: halothane, fluorothane
- Dose-related—risk and severity increase with dose
  - Cholestasis: testosterone, oral contraceptives
  - Hepatocellular injury: carbon tetrachloride, acetaminophen

Liver Labs: Bilirubin
- Byproduct of heme metabolism
  - Hemoglobin -> biliverdin -> unconjugated (indirect) bilirubin -> conjugated (direct) bilirubin -> urobilinogen
- Unconjugated: insoluble, albumin-bound form
  - Not secreted in urine
- Conjugated: soluble glucuronidated molecules
  - Physiologically secreted in bile
  - Presence in blood and urine is pathologic (indirect:direct normal 5-10:1)
- Urobilinogen (gut flora by-product) is H₂O soluble
  - 80% excreted in feces
  - 20% reabsorbed; mostly enters enterohepatic circulation
  - small amount physiologically excreted in urine
Liver Labs: Hyperbilirubinemia
• All forms cause jaundice, icterus (apparent at >2mg/dL)
• Unconjugated is neurotoxic, especially to infants (kernicterus)
• Hemolysis
  – Increased heme release leads to unconjugated hyperbilirubinemia
  – Normal liver function, so conjugated bilirubin is excreted, and does not appear in the blood
  – Increased delivery to intestine leads to increased urinary urobilinogen
  – Increased bilirubin delivery to gallbladder leads to pigmented gallstones

Liver Labs: Hyperbilirubinemia (Continued)
• Biliary obstruction
  – Conjugated bilirubin is not excreted in feces, and levels increase in blood and urine (>50% conjugated bilirubinemia suggests obstruction)
  – Decreased intestinal delivery leads to decreased urinary urobilinogen
  – Bile salts not excreted in stool, resulting in increased blood levels and deposition in skin; causes acholic stool and pruritis

Liver Labs: Hyperbilirubinemia (Continued)
• Hepatocellular injury
  – Liver cannot properly conjugate bile, leading to unconjugated hyperbilirubinemia
  – Injured hepatocytes lose membrane integrity, so conjugated bilirubin spills into blood; however, levels of conjugated bilirubin are still much lower than levels of unconjugated bilirubin
  – Appears with increase in liver enzyme levels and signs of liver failure

Liver Enzymes
• Aspartate aminotransferase (AST/SGOT), Alanine aminotransferase (ALT/SGPT)
  – Necrosis of tissue releases enzymes into blood
  – Highest levels in acute necrosis; persistent elevation in chronic disease
  – ALT more specific for liver than AST
• Alkaline Phosphatase
  – Increase signifies injury or proliferation of bile duct epithelium
  – Electrophoresis separates from bone remodeling isoform
• γ-glutamyltransferase (GGT)
  – Highest in extrahepatic obstruction (5-30X); mild elevation with infectious hepatitis (2-5X)
  – Extremely sensitive for hepatobiliary disease
  – Earliest to increase and remains elevated

Liver Labs – Other Markers
• Increase in PT and/or aPTT can be due to EITHER
  – Decreased vitamin K absorption due to fat malabsorption (bile deficiency, intestinal damage) or intestinal floral derangement
  – Decreased clotting factor synthesis (severe liver damage)
• Decreased albumin
  – Normally synthesized by liver to increase plasma oncotic pressure
  – Decrease causes anasarca and is a poor prognostic sign
• Hyperammonemia
  – Impaired urea cycle metabolism
  – Leads to hepatic encephalopathy, hyperreflexia, asterixis
• Elevated serum lipids (cholesterol, TGs)
  – Impaired hepatic lipid metabolism

Liver failure, liver infarction
• 2 most common causes – viral hepatitis and ethanol
• Can occur acutely or gradual accumulation of damage
  – Need to lose 80-90% of function before “failure”
• Loss of protein synthesis
  – Serum albumin, coagulation components
  – Can measure with PTT, CBC
• Loss of metabolic functions
  – Hyperestrogenism – most common cause of gynecomastia
  – Palmar erythema, telangiectasias, weight loss, muscle wasting, hypoglycemic, fetor hepaticus
• Hepatorenal failure - no intrinsic renal damage
Liver failure, liver infarction

- Hepatoencephalopathy – CNS, neuromuscular system
  - Buildup of toxic products, shunting of blood
- Ischemia rare – dual blood supply
- Infarctions generally localized
- Typically anemic and pale-tan, can be hemorrhagic
- Associated with hepatic artery thrombosis, PAN, embolism, neoplasia or sepsis
- Portal vein thrombosis – abdominal pain, ascites, portal hypertension, bowel obstruction, bowel infarction
- Extrahepatic – cancers, sepsis, post surgical
- Intrahepatic – infarct of Zahn – sharp line of red/blue discoloration

Liver Disease in Pregnancy

- **Pre-eclampsia** causes periportal necrosis (hepatic hematoma when severe) and the subclinical HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
- **Acute fatty liver** of pregnancy is microvesicular steatosis during third trimester, due to metabolic defects...can cause hepatic failure
- **Intrahepatic cholestasis** often causes pruritis (bile salts in skin)...benign except gallstone risk
- Termination of pregnancy cures all three

Hepatocellular Carcinoma

- In US, alcoholic cirrhosis, HCV, hemochromatosis biggest factors... HBV worldwide
- Gross: may be unifocal, multifocal, or diffuse
- Well-differentiated tumors form nests with central lumen, or carcinoma may be anaplastic
- Strong propensity for vascular invasion...intrahepatic and IVC metastasis
- Symptoms masked by underlying hepatitis/cirrhosis...α-fetoprotein elevated 50-75%, imaging most important diagnostically

Cholangiocarcinoma

- Malignancy in biliary tree, arising either intra- or extrahepatic
- Increased risk with primary sclerosing cholangitis, Caroli disease, and choledochal cysts
- Sclerosing well-differentiated adenocarcinomas that invade lymph and sinusoids, causing extensive intrahepatic metastasis...like normal biliary epithelium, do not stain for bile
- Late symptomology (bile obstruction; lung, vertebral, adrenal, brain metastasis) and poor prognosis

Portal HTN, Congestive Liver Disease

- Pressure difference of 5mmHg b/w Portal and hepatic vv.
- Causes:
  - Prehepatic—portal and splenic vv. thrombosis
  - Intrahepatic—CIRRHOSIS, schistosomiasis (3rd world)
  - Posthepatic—R Heart failure, Budd-Chiari syndrome
- Sx—collaterals (caput medusa, esophageal varices, hemorrhoidal plexus), ascites, hepatic encephalopathy

Intrahepatic Congenital Biliary Disease

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**Congenital Hyperbilirubinemia**

- **Unconjugated**
  - Gilbert syndrome is most common: defect in uptake/conjugation of unconjugated bilirubin
  - Usually mild or asymptomatic
  - Crigler-Najjar syndrome: decreased conjugating enzymes
    - Type 2 is fatal

- **Obstructive (Conjugated)**
  - Dubin-Johnson: defect in secretion into intrahepatic ducts, see black pigment in hepatocytes
  - Rotor’s Syndrome, like Dubin-Johnson but no black pigment

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**Extrahepatic Congenital Biliary Disease**

- **Biliary Atresia**: complete obstruction of bile flow due to destruction of all/part of extrahepatic bile ducts
  - born with normal ductal system, destroyed over weeks to months
  - periductal inflammation and fibrosing stricture of hepatic/common bile duct
  - causes multiple: viruses, toxins, autoimmune, genetics
  - leads to cholestasis & rapidly progressing secondary biliary cirrhosis
  - ↑ bilirubin, modest ↑ transaminase & ALP
  - -#1 cause of death due to liver disease in early childhood

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**Extrahepatic Congenital Biliary Disease**

- **Choledochal cysts**: congenital dilations of common bile duct
  - present before age 10 w/ jaundice, recurrent colicky abdominal pain
  - may exist in conjunction with cystic dilations of intrahepatic biliary tree (caroli’s disease)
  - multiple forms: segmental cylindrical dilations; diverticuli; choledochocoles (cystic lesions protruding into duodenum)
  - ↑ risk for stones, stenosis, stricture, intrahepatic ductal disease, bile duct carcinoma

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**Primary Biliary Cirrhosis**

- **Autoimmune destruction of the intrahepatic bile ducts**
- Females >> males, middle-age, insidious onset
- Symptoms from bile obstruction: pruritis, jaundice, dark urine, light acholic stools, xanthomas, hepatosplenomegaly
- **Laboratory**:
  - Conjugated hyperbilirubinemia
  - increased serum alkaline phosphatase, bile acids & cholesterol
  - Elevated serum anti-mitochondrial IgM antibodies
- May be symptom free for many years, but w/ time (2 or more decades) destruction of liver architecture & portal tract fibrosis leads to cirrhosis and portal HTN

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**Secondary Biliary Cirrhosis**

- **Intrahepatic** biliary destruction secondary to long-standing extra-hepatic biliary tree obstruction:
  - Gallstones, strictures, carcinoma of pancreatic head, biliary atresia (kids)
- Same symptoms and lab values as primary biliary cirrhosis but w/out the increase in serum IgM
- **Morphology**:
  - Prominent bile stasis in bile ducts & formation of bile lakes
  - Green bile pigment staining of hepatic parenchyma
  - Proliferation of ductal epithelium with surrounding neutrophilic infiltrate, portal tract edema and feathery hepatocyte degeneration
  - Eventual periportal fibrosis & micronodular cirrhosis
Primary Sclerosing Cholangitis

- Inflammation and obliterative fibrosis of both intrahepatic & extrahepatic bile ducts
- Male > female, 3rd-5th decades, possibly autoimmune, 50-70% associated w/ ulcerative colitis, “Walter Payton disease”
- Same insidious onset, same symptoms and labs as primary biliary cirrhosis, but with autoantibodies in <10%
  - Over time, leads to cirrhosis & portal HTN like 1° & 2° biliary cirrhosis
- Increased risk of cholangiocarcinoma
- Morphology:
  - Concentric periductal portal tract fibrosis ➔ onion-skinning
  - Lymphocytic infiltrate
  - Segmental stenosis of extra & intrahepatic bile ducts ➔ “beading” on xray

Gallbladder Cholelithiasis

- Clinical correlations
  - Obesity, genetic predisposition, high caloric diet, high cholesterol, GI disorders (cystic fibrosis), female sex hormones, age, diabetes
  - Increasing incidence with age; significant proportion of women in their 50’s have stones at autopsy
- Symptomology: fatty food intolerance, colic, infections, mucosal erosions with perforation and fistula formation
- Cholesterol stone formation
  - Cholesterol stones: radiolucent, large (several cm.)
  - Bile must be supersaturated with cholesterol
- Pigmented gallstones: increased hemolysis and delivery of unconjugated bilirubin to liver
  - Jet black ovoids; associated with Oriental race, chronic hemolysis, ETOH

Gallbladder Cholecystitis

- Cause: 90% are due to gallstones; ischemia
- Pathogenesis:
  - Protective mucus layer is disrupted ➔ dysmotility ➔ distention and increased intraluminal pressure ➔ decreased blood flow; may later develop infection
- Pathology:
  - Emphyema of the gallbladder: lumen filled with pus
  - Hydrops of the gallbladder: atrophic chronically obstructed gallbladder containing clear secretions
  - Mild: wall is thickened, edematous, hyperemic
  - Severe: gangrenous with perforations
- Clinical:
  - RUQ pain, fever, nausea, vomiting, leukocytosis
  - Complications: ascending cholangitis, perforation and abscess formation, rupture and peritonitis, biliary enteric fistula

Biliary Cancers

- Cholangiocarcinoma
  - Adenocarcinomas of the ductules; <10% of hepatic carcinomas
  - Clearly defined glandular and tubular structures; markedly desmoplastic with mucus in cells
  - Associated with primary sclerosing cholangitis, inflammatory bowel disease (particularly ulcerative colitis), and choledochal cysts
  - Not associated with cirrhosis or chronic hepatitis
  - Hematogenous spread to lungs, bone, adrenals, brain; lymph nodes in 50%

- Ductal Carcinoma
  - M>F; assoc. with chronic inflammation; ascarsis and liver flukes, Oriental pop.
  - Also associated with primary sclerosing cholangitis, inflammatory bowel disease, or choledochal cysts
  - Uncommon tumors, extremely insidious
  - Gallstones present only in 1/3
  - 75% metastasize before discovery
    - Due to development of jaundice, may be relatively small at diagnosis
    - However, most not resectable at time of surgery

Acute Pancreatitis

- Autodigestion of the pancreas by pancreatic enzymes
- Cause: alcohol (65% of cases; men) and gallstones/biliary disease (35-60%; women) are primary risk factors
- Pathology:
  - Edema, fat necrosis, inflammation, proteolytic destruction of parenchyma, destruction of blood vessels with hemorrhage, pseudocyst formation
  - No fibrosis
- Clinical
  - Serum amylase and lipase will be increased
  - Jaundice, severe abdominal pain
  - Hypocalcemia can result due to Ca++ collecting in Ca++ soaps
Chronic Pancreatitis

- Chronic pancreatitis is usually secondary to repeated exacerbations of subclinical acute pancreatitis
- Almost always associated with alcohol abuse. Also biliary disease, elevated Ca++, elevated lipids
- Pathology
  - Inflammation with destruction of exocrine pancreas, fibrosis, and later destruction of endocrine parenchyma
  - Calcification (often visible on x-ray)
  - Dilated ducts with protein plugs
- Clinical
  - Fat malabsorption may occur (Vit A, D, E, K)
  - Clinical signs: variable, but include abdominal/back pain and steatorrhea
  - May have repeated exacerbations or remain subclinical until the development of pancreatic insufficiency or diabetes mellitus
  - Amylase and lipase may not be elevated due to destruction of acini

Pancreatic Pseudocysts and Islet Cell Tumors

- Pseudocysts
  - Occur at locations of inflammation, necrosis, or hemorrhage (e.g. acute pancreatitis)
  - Usually solitary and located at tail (unilocular = cyst, multilocular = cancer)
  - Necrotic, hemorrhagic material rich in pancreatic enzymes surrounded by granulation tissue
  - No epithelial lining or communication with ducts
  - Usually spontaneously resolve; Can cause abdominal pain, peritonitis, and hemorrhage
- Benign tumors of islet cells can cause insulinoma, gastrinoma (Zollinger-Ellison), glucagonoma, pancreatic carcinoid tumor, etc...

Pancreatic Cancer

- Almost always adenocarcinoma. >99% ductal.
- Associated w/ smoking, diet, industrial toxins, not alcohol
- Clinical
  - Often arises in pancreatic head → jaundice
  - Involvement of pancreatic tail → 2° diabetes
  - Abdominal pain radiating to back, anorexia, migratory thrombophlebitis (Trousseau sign), distended gall bladder
- Histology
  -Ranges from well-differentiated glandular adenocarcinomas to anaplastic cuboidal epithelium
  - Deeply infiltrative growth
  - Strong desmoplastic response
- Silent and widespread dissemination (massive hepatic metastasis). <1 yr survival.
Kidney Vascular and Congenital

- **Complete or bilateral renal agenesis:**
  - Rare condition, not compatible with life (stillborn infants)
  - Both kidneys are absent.
  - Results in oligohydramnios (decreased amniotic fluid), which occurs because the renal system fails to excrete fluid swallowed by the fetus.
  - Multiple fetal anomalies all caused by oligohydramnios and collectively known as the oligohydramnios, or Potter sequence.

- **Unilateral renal agenesis:**
  - One kidney is missing.
  - Much more common than complete renal agenesis.
  - Contralateral kidney undergoes hypertrophy with progressive glomerular sclerosis.

Kidney Vascular and Congenital

- **Renal ectopia:**
  - Abnormal location of a kidney, frequently in the pelvis.

- **Horseshoe kidney:**
  - The most common congenital kidney disorder
  - Occurs when kidneys are fused at lower pole.
  - As the kidneys ascend during development they frequently catch on the inferior mesenteric artery.
  - Fusion often results in obstruction or infection because of impingement on the ureters.

Renal - Vascular

- **Benign hypertension**
  - Slightly small kidneys
  - Hyaline arteriolosclerosis

- **Malignant hypertension**
  - Rapidly progressive severe HTN
  - Necrotizing arteriolitis
    - *Fibrinoid necrosis*
  - Hyperplastic arteriolosclerosis

Renal Artery Stenosis

- **Renal artery stenosis**
  - Atherosclerosis
  - Uncommon cause of hypertension (2-5%), (not renal failure)
    - Constriction of one renal artery results in stimulation of renin
    - Potentially curable by surgical intervention

- **Fibromuscular dysplasia of the renal artery**
  - Fibromuscular thickening of the intima, media, or adventitia
  - More common in women and at a younger age (3rd-4th decades)
  - May be single well-defined constriction or series of constrictions in middle or distal portion

- **Ablative changes in normal kidney**
  - Arteriolosclerosis from the hypertension, focal segmental GN

Fibromuscular dysplasia

- **Fibromuscular dysplasia is a hyperplastic disorder that is usually bilateral, occurs in females, and primarily affects the carotid and renal arteries. Abdominal bruits are commonly heard.**

- **Fibromuscular dysplasia leads to renal artery stenosis, which leads to HTN and possible renal infarction. Renal infarction reduces nephron number, causing increased salt-sensitivity and further increase in HTN.**
Kidney Vascular and Congenital

Kidney Vascular and Congenital

**Kidney Vascular and Congenital**

- **Atheroembolic Renal Disease:**
  - Atheroembolic renal disease occurs when a piece of plaque from the aorta and/or other large arteries breaks off and travels through the bloodstream, blocking small renal arteries. Because renal blood supply has no collaterals, embolic obstructions are prone to producing infarcts which result in a decreased GFR and unilateral renal atrophy.
  - Atheroembolic renal disease is a common cause of renal insufficiency (poor kidney function) in the elderly.

- **Renal Artery Aneurysm:**
  - A renal artery aneurysm is a bulging, weakened area in the wall of an artery to the kidney.
  - Most of these aneurysms are small (less than two centimeters, or about three-quarters of an inch) and without symptoms.
  - Renal artery aneurysms are uncommon, and are generally discovered during diagnostic procedures performed in relation to other conditions.

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**Autosomal Dominant Polycystic Kidney Disease**

- Bilaterally enlarged kidneys with multiple expanding cysts that ultimately destroy the parenchyma.
- **Pathology**
  - External surface appears to be composed entirely of cysts up to 3-4 cm.
  - Microscopically functioning nephrons exist between cysts.
  - Cysts arise from tubules and therefore have variable lining epithelium.

---

**Autosomal Recessive Polycystic Kidney Disease**

- **Pathology**
  - Bilaterally enlarged kidneys with smooth external surface.
  - On cut section, small cysts in cortex and medulla give kidney a spongeliike appearance.
  - Dilated channels at right angles to the cortical surface.
  - Cysts originate from collective tubules and are lined by uniform cuboidal cells.
  - Liver: epithelium lined cysts and proliferation of bile ducts.

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**Autosomal Dominant Polycystic Kidney Disease**

- Clinical:
  - Presentation (variable): 15-30 years old, flank pain, hypertension, hematuria, progressive renal failure.
  - Large lesions are palpable.
  - 40% have cystic disease of the liver (most common), spleen, pancreas, brain.
  - Berry aneurysms in circle of Willis.
  - 20% have mitral valve prolapse or other valvular abnormalities.
  - No increase in renal cell carcinoma.
  - Death due to uremia or hypertension.

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**Autosomal Recessive Polycystic Kidney Disease**

- Clinical:
  - Prenatal and neonatal forms are fatal in infancy.
  - Often due to pulmonary hypoplasia caused by oligohydramnios (also causes flattened facies, deformities of feet).
  - Hepatic disease predominates in older children (may develop portal hypertension with splenomegaly).
Other Cystic Kidney Disease

- Multicystic renal dysplasia
  - Most common, sporadic
  - Persistence in the kidney of abnormal structures including islands of cartilage, undifferentiated mesenchyme, and immature collecting ducts, with abnormal lobar organization
  - Unilateral or bilateral
  - Cysts and kidneys are variably sized
  - No liver disease

- Medullary sponge kidney
  - Present to some degree in up to 1% of population
  - Cystic dilation of papillary ducts of the medulla
  - Bilateral in 70%; not all papillae are affected
  - Calcium oxalate crystals present in dilated collecting ducts
  - Stones, infection, or recurrent hematuria in 3rd or 4th decade
  - Acquired
    - Associated with long-term dialysis
    - Cortical and medullary cysts; often contain calcium oxalate crystals
    - Increased incidence of transitional cell carcinoma
    - Usually asymptomatic

Nephrotic Syndrome

- Syndrome of Glomerular dysfunction that is characterized by increased loss of proteins in the urine due to increased basement membrane permeability
- CLINICAL MANIFESTATIONS
  - Massive proteinuria without hematuria (>3.5g/day)
  - Hypoalbuminemia (<3g/dl)
  - Generalized edema – Due to ↓ plasma oncotic pressure
  - Periorbital edema
  - Hypertension! & Activation of the Renin/Angiotensin System
  - Hyperlipidemia and Hypercholesterolemia – due to loss of lipoproteins and alterations in liver production of lipoproteins
  - Hyperlipiduria and Oval Fat Bodies
  - Increase in Infections due to loss of low weight globulins and complement
  - Loss of anticoagulants → hypercoagulable state

Nephrotic Syndrome Disorders

- Minimal Change Disease
  - Most common cause of Nephrotic Syndrome in Children 2-6 yrs.
  - Treated with steroids
  - Pathology
    - diffuse loss of foot processes of epithelial cells (visceral epithelial injury)
    - no changes seen by light microscopy
    - tubules are laden with lipid (secondary to hyperlipidemia) = ‘lipid nephrosis’
    - severe SELECTIVE proteinuria with no loss of renal function: no hypertension or hematuria (Hypoalbuminemia)
    - Resolves when children reach adolescence. Adults are slower to respond,
    - in adults, associated with Hodgkin’s disease, lymphoma, leukemia
    - also secondary to NSAID therapy with acute interstitial nephritis

- Membranous Glomerulonephritis
  - Occurs with chronic antigen-antibody mediated disease
  - Pathology
    - uniform, diffuse thickening of the glomerular capillary wall
    - irregular dense SUBEPITHELIAL deposits of IgG and C3 between BM and epithelial cells with loss of foot processes
    - markedly thickened, irregular membrane
  - Clinical
    - nephrotic syndrome, hematuria, hypertension
    - progression results in sclerosis of glomeruli, rising BUN, relative reduction of severity of proteinuria, and development of hypertension
  - course variable; treat underlying condition

- Focal Segmental Glomerulosclerosis
  - Minority of the glomeruli (focal); Sclerosis involving segments within glomeruli (segmental)
  - Pathology
    - focal detachment of the epithelial cells with denudation of the underlying GB membrane
    - hyaline thickening of afferent arterioles
    - IgM, C3 deposition in mesangium
    - accompanied by renal ablation for segmental glomerulosclerosis with tubular atrophy and interstitial fibrosis
  - Associated with
    - HIV/AIDS
    - Dysfunction of podocyte slit diaphragms in glomerular BM; dysfunction of nephrin and podocin caused by cytokines or toxins
  - Nonresponsive to corticosteroids
Membranous Glomerulonephritis
- Most common nephrotic syndrome in adults
- **Etiology:** Idiopathic, drugs (NSAIDS), Carcinomas, Autoimmune disorders (nephrotic presentation of SLE), Infections (chronic hep B, hep C, syphilis, malaria)
- **Pathogenesis:** Type III hypersensitivity with complement activation.
  - subepithelial immune complex deposits “lumpy bumpy” appearance on immunofluorescence
  - complement activation damages glomerular membrane to produce nonselective proteinuria
  - Basement membrane is laid down over immune complex deposits leading to membrane thickening
- **Light microscope** shows diffuse thickening of the *glomerular capillary wall* throughout the entire glomerulus
- **Electron Microscope** shows: “spike and dome appearance” with silver stains

Nephritic Syndrome
- Damage to the glomeruli leading to the formation of holes in the basement membrane. Results in damaged glomerular apparatus and subsequent bleeding into Bowman’s space
- **Clinical Symptoms:**
  - Oliguria (due to decreased GFR)
  - Azotemia (elevated creatinine and BUN)
  - Hypertension (due to retention of salt)
  - Proteinuria >150mg but <3.5g
  - BUN/Creatinine level of >15
  - Hematuria – best defined as *red cell casts* and RBC with dysmorphic membranes
  - Commonly defined as “smoky brown urine”

Acute Proliferative
- Post-streptococcal GN
  - 1-2 weeks following Strep pyogenes infection
  - Malaise, nausea, fever, dark brown urine
  - Serum anti-streptolysin O (ASO) titer
  - Acute proliferative glomerulonephritis with glomerular hypercellularity, neutrophils
    - hypercellularity due to infiltration by leukocytes, and proliferation of endothelial and mesangial cells
  - Linear deposition of IgG and complement; subepithelial humps on EM
  - activation of complement is associated with low serum complement levels
  - immunofluorescence shows granular deposits of immunoglobulin, complement
  - resolves with conservative therapy; rarely progresses to RPGN (more often adults)

Rapidly Progressive (Crescentic) Glomerulonephritis
- Characterized by rapidly declining renal function and onset of renal failure within weeks
- Presence of distinctive crescents made of infiltrating leukocytes, proliferating epithelial cells, and fibrin in most of glomeruli
- Obliteration of Bowman’s space & compression of glomerular tuft
- Eventual crowding out of the glomeruli = renal failure
- Fibrin strands are prominent between the cell layers and crescents
- Distinct ruptures of the BM
- Usually immune-mediated injury
  - type I – idiopathic, Goodpasture’s syndrome
  - type II – immune complex-mediated
  - type III – “pauci-immune” with anti-ANCA antibodies (Wegener’s, microPAN)

Membranoproliferative Glomerulonephritis
- Characterized by hypercellular glomeruli caused by mesangial and endothelial cell proliferation and leukocyte infiltration
- “tram track” appearance of the capillary wall caused by reduplication of glomerular basement membrane
- Two Types
  - Type I
    - granular deposits of complement with or without immunoglobulin
    - Subendothelial electron-dense deposits
  - Type II
    - C3 Nephritic factor; IgG usually absent (alternative pathway)
    - Prominent electron-dense deposits along the lamina densa within the basement membrane (splitting of basement membrane)
    - Features of nephritis and protein loss; hypocomplementemia
- Chronic immune complex disease, SLE

IgA Nephropathy (Berger’s Disease)
- frequent cause of recurrent gross or microscopic hematuria
  - mild proteinuria is seen and nephrotic syndrome may develop
- Characterized by IgA deposition within the mesangium
- Often seen after respiratory, gastrointestinal, or urinary tract infection in children and young adults
- Lesions vary considerably
  - focal proliferative glomerulonephritis
  - focal segmental sclerosis
  - crescentic glomerulonephritis
Diabetic Nephropathy

- Characterized by glomerulosclerosis and a range of nephropathies
  - non-nephrotic proteinuria, nephrotic syndrome, & chronic renal failure
- Also causes
  - arteriolar sclerosis
  - increased susceptibility to infection (papillary necrosis/Acute pyelonephritis)
  - tubular lesions
- Pathogenesis
  - thickened basement membrane and increased mesangial matrix
  - Increased amount and synthesis of collagen type IV and fibronectin
  - nonenzymatic glycosylation of proteins

Diabetic Nephropathy: Pathology

- Capillary basement membrane thickening
  - diffuse glomerulosclerosis
    - diffuse increase in mesangial matrix with PAS positive deposit
    - continuous with hyaline thickening of arterioles
  - nodular glomerulosclerosis (Kimmelstiel-Wilson disease)
    - ovoid or spherical hyaline masses situated in the periphery of the glomerulus that lie within mesangial core
    - uninvolved lobules and glomeruli all show striking diffuse glomerulosclerosis
  - arteriolosclerosis – both afferent and efferent (in hypertension, only afferent)
  - ischemic tubular atrophy, interstitial fibrosis, and contraction in size of kidneys

Renal Amyloidosis

- Renal Amyloidosis
  - Subendothelial and mesangial amyloid deposits
    - Eventually obliterate glomeruli
  - Amyloid can be identified by special stains such as Congo Red and have bipolarized birefringence under polarized light
  - May present with nephrotic syndrome
  - Kidney size is normal or enlarged
  - Light. Assoc with Chronic Inflammatory Diseases like RA, Multiple Myeloma

Alport Syndrome

- Mainly X-linked recessive disorder involving defective GBM synthesis via abnormal Type IV collagen production
  - Mutation in α-5 chain of type IV collagen
-Occurs in Adolescent or adult males by age 50
  - presents with nephritic syndrome, nerve deafness, lens dislocation and/or cataracts
  - Dark colored urine (hematuria), mild proteinemia
- Pathology
  - Irregular BM thickening and splitting of the lamina densa
  - Foamy change in tubular epithelial cells
  - Glomerular basement membrane shows attenuation with splitting of the lamina densa on EM
- Progress to chronic renal failure in adulthood

HUS/TTP of the kidney

- Causes of HUS/TTP are variable but all result in:
  - Endothelial injury/activation → intravascular thrombosis
    - capillaries/arterioles
    - Platelet aggregation
  - Thrombi in renal vessels/glomeruli → renal failure
  - Childhood HUS
    - E. coli 0157:H7 → verocytotoxin damages endothelium
    - Sudden onset hematemesis and melana, servere oliguria, hematuria, microangiopathic hemolytic anemia, neurologic changes
    - Kidney morphology: patchy or diffuse cortical necrosis, thickening/splitting of glomeruli capillary walls with fibrin deposits

HUS/TTP of the kidney continued

- Adult HUS
  - Initial insult results from: infection (endotoxin/shiga toxin), antiphospholipid syndrome (SLE), placental hemorrhage w/ pregnancy, vascular renal disease, chemotherapy or immunosuppressive drugs
- Idiopathic TTP
  - Fever, neurologic symptoms (distinguishes TTP from HUS), hemolytic anemia, thrombocytopenic purpura
  - Genetic defect of enzyme involved in von Willebrand factor cleavage
  - CNS involvement dominates: renal involvement only 50% of time
Acute Tubular Necrosis

- Most common cause of acute renal failure
- Acute focal tubular epithelial necrosis
  - Sudden lack of perfusion – crush injury, car accident
  - Exposure to toxic agents – Gentamicin, carbon tetrachloride, ethylene glycol, methanol, radiographic contrast agents
  - Ischemic changes – normal components of cell injury
    - Cell detachment, granular casts with Tamm-Horsfall protein
    - Changes are reversible, can have complete regeneration
    - Depends on integrity of tubular basement membrane

- 3 clinical phases – symptoms depend on degree of damage
  - Initiation – decline in urine output, increase in BUN
  - Maintenance – decreased GFR, U/O – increased Na+, K+, water
  - Recovery – increase in output → cannot concentrate urine

Interstitial Nephritis

- Caused by sulfonamides, penicillins, ampicillins, cephalosporins, fluoroquinolones, isoniazid, rifampin, NSAIDs, loop diuretics
- Occurs 2 weeks after drug use
- Maculopapular or diffusely erythematous rash, fever, eosinophils
- Mild proteinuria and hematuria
- Positive leukocyte esterase

Tubulointerstitial Disease

- Interstitial Nephritis
  - Sulfonamides, penicillins, ampicillins, cephalosporins, fluoroquinolones (cipro, norfloxacin), isoniazid, rifampin, NSAIDs, loop diuretics
  - 2 weeks after use of the drug
  - Maculopapular or diffusely erythematous rash, fever, eosinophils
  - Eosinophils in urine
  - Mild proteinuria and mild hematuria
  - Leukocyte esterase
- Nephrocalcinosis due to hypercalcemia
  - Loss of concentrating ability
  - Progressive loss of renal function
  - Source of hypercalcemia
    - Metastatic disease to bone
    - May also have calcium oxalate stones

Renal Cell Carcinoma

- Present with painless hematuria, flank mass, CVA tenderness
- Male dominant – 6th to 7th decade
- Risk factors: smoking, von Hippel-Lindau disease
- Yellow mass in upper pole with cysts and hemorrhage
- Microscopic clear cells that contain glycogen and lipids
- Tendency to invade renal vein – possibly to IVC and R heart
- Mets to: lung> lytic bone lesions> LN> liver/adrenal> brain
- Ectopic secretion of:
  - EPO → polycythemia
  - Parathyroid-related peptide → hypercalcemia

Wilms Tumor

- Most common primary renal tumor in children
- Derived from mesonephric mesoderm
- Large, solitary well-circumscribed mass
  - necrotic gray-tan homogeneous tumor
  - Cyst formation and focal hemorrhage
  - Recapitulation of different stages of nephrogenesis
  - Bilateral and multicentric tumors associated with familial disease
- 2 hit hypothesis
  - Premalignant nephroblastomatosis followed by 2nd genetic insult
- Present with large, palpable abdominal mass in 2-5 year old
  - Hematuria after trauma, intestinal obstruction, hypertension
Urothelial (transitional cell) carcinomas of renal pelvis

- 5-10% of primary renal tumors
- benign papillomas to frank papillary carcinomas
- because they lie within pelvis, discovered when small
  - early symptomology includes obstruction, hematuria, and fragmentation of tumor
- analogous to tumors of bladder, urinary tract
- may be multiple
- associated with analgesic nephropathy
- infiltration of wall of pelvis and calyces; prognosis is not good

Renal - Infection

- Ascending Infection – E. coli; UT abnormalities
- Hematogenous dissemination
  - Patient ill with sepsis, or other site of infection
  - Wedge-shaped regions of yellow-white cortical necrosis
- Acute pyelonephritis
  - Fever, leukocytosis
  - Flank, CVA pain
  - WBC and WBC casts
  - Vesicourethral reflux important
  - E coli most common organism (non-obstructed)

Renal - Infection

- Chronic pyelonephritis
  - Reflux nephropathy; vesicoureteral reflux
  - Coarse, irregular scarring
  - Blunting and deformity of calyces
  - Assymetric involvement of the kidneys
  - Loss of tubules with loss of concentrating ability resulting in polyuria
  - Inflammatory infiltrates (lymphocytes, plasma cells, neutrophils)
  - Interstitial fibrosis
  - Involvement of collecting systems, hydronephrosis may cause thinning of cortex

Urinalysis

- Specific gravity
  - A normal specific gravity is between 1.01-1.025. It reflects the ability of the kidneys to concentrate urine.
  - The first sign in renal disease is a persistent SG <1.01
- pH
  - The kidneys maintain a normal acid-base balance by reabsorbing a variable amount of sodium ions by the tubules and tubular secretion of hydrogen and ammonium ion exchange.
  - An acid urine with a pH < 6 can be seen in patients on a high protein diet, in acidosis, uncontrolled diabetes mellitus, and renal tubular acidosis.
  - An alkaline urine may be found either with urinary tract infections (Proteus) or possible bacterial contamination of an old specimen with urea-splitting organisms.

Urinalysis

- Protein:
  - Minimal proteinuria- (< 0.5 grams per day)- associated with glomerulo-nephritis, polycystic disease of the kidneys, renal tubular disorders, the healing phase of acute glomerular nephritis, and latent or inactive stages of glomerulonephritis.
  - Moderate proteinuria, (0.5 grams to 3.5 grams per day) may be found in the vast majority of renal diseases, such as mild diabetic nephropathy, and chronic glomerulo-nephritis.
  - Severe proteinuria, (> 3.5 grams per day) is significant for nephrotic syndrome. It can also bee seen in nephrosclerosis, amyloidal disease, systemic lupus erythematosus, renal vein thrombosis and congestive heart failure.

Urinalysis

- Glucose: the threshold of blood glucose is 250 mg percent. When glucose exceeds this number, the glucose transporters or the PCT saturate and sugar overflows into the urine. Glucose should not be found in the urine normally (except in pregnancy which will decreases the saturation capacity of glucose in the PCT)
- Bilirubin: the presence may suggest hepatocellular disease versus the presence of hepatobiliary obstruction or viral hepatitis
- Urobilinogen: small amounts are normal in the urine. An increase may be indicative of liver disease, congestive heart failure, or hemolytic anemia. An absence of urobilinogen indicates hepatobiliary obstruction
Urinalysis

- **Nitrites**: usually sensitive for nitrogen releasing bacteria (E.Coli). Bacteria reduce nitrates to nitrite via a reductase enzyme.
- **Leukocyte esterase**: released from neutrophils in response to bacterial infections of the GU tract, sign of infection. (Urinalysis with positive Leukocyte esterase but negative bacterial cultures--> chlamydia).
- **Casts**: indication of tubular damage.
  - RBC casts =glomerular inflammation (nephritic syndromes)
  - WBC casts =tubulointerstitial nephritis, acute pyelonephritis, glomerular disorders.
  - Granular ("muddy brown") casts = acute tubular necrosis.
  - Waxy cast =often very broad, are a sign of chronic renal failure.
  - Hyaline casts =nonspecific and often naturally occurring.
  - Fatty casts = nephrotic syndrome

- **Color**: affected by concentration of urine. Darker urine indicates either highly concentrated urine or the presence of bilirubin. Red urine indicates blood or myoglobin. Bright yellow urine may be secondary to vitamin intake.
- **Turbidity**: normal urine is clear. Amorphous phosphates or amorphous urates may cause urine to appear more cloudy or hazy.
- **Red blood cells**: normal should be 0-2. > 2 red blood cells may indicate trauma (stone), menstruation, infection, cancer, or nephritic syndrome.
- **White blood cells**: > 5-10 white blood cells may be an indication of inflammation or infection.

Renal Obstructive Disease

- **Obstruction** → ↓ urine flow → ↑ medullary pressure → ↓ tubular function → ↓ GFR
- **Complications**:
  - Hydronephrosis
  - Interstitial inflammation and fibrosis
  - Urinary stasis: ↑ d susceptibility to infection, stone formation
  - If chronic: pressure atrophy with cortical thinning and degeneration of the medullary pyramids
- **Types**:
  - Unilateral: may be asymptomatic until late
  - Partial bilateral: polyuria, dilute urine, salt wasting, tubular acidosis
  - Complete bilateral: oliguria, anuria

Renal Obstructive Disease- Urolithiasis

- **Urolithiasis** – stones formed with supersaturation state; favored by low urine volume and stasis; most unilateral (80%)
- **4 main stone types**:
  - 75% calcium (calcium oxalate) **radiopaque**
  - 15% triple or struvite (Mg ammonium phosphate)
  - 6% uric acid **radiolucent**
  - 1-2% cystine
- **Ca oxalate stone in presence of↑ uric acid secretion** = hyperuricosuric calcium nephrolithiasis
- **Struvite stones formed after infection by urea-splitting bacteria** (e.g. Proteus and staph) → "staghorn" largest

Renal Obstructive Disease- Pyelonephritis

- **Acute bacterial**
  - 85% gram neg bacteria (E. coli)
  - Nosocomial: Klebsiella, Pseudomonas
  - Symptom: CVA tenderness, WBC casts, nitrites in urine
- **Chronic bacterial**
  - Often due to vesicoureteral reflux or obstruction
  - Thyroidization: tubules w/ colloid cast
  - Focal segmental glomerulosclerosis
- **Xanthogranulomatous pyelonephritis**
  - Foamy macrophages and plasma cells
  - Associated w/ Proteus infections
Lower Urinary Tract - Other

- **Hemorrhagic cystitis**
  - Due to radiation or cytotoxic drugs (cyclophosphamide)
- **Chronic obstruction**
  - Leads to bladder hyperplasia, diverticuli, and trabeculae
- **Vesicoureteral reflux**
  - Improper insertion angle of ureter into bladder
- **Cystitis cystica/glandularis**
  - Cell nests form cystic structures in bladder wall
  - Glandularis: Colonic type metaplasia with goblet cells
    - May predispose to adenocarcinoma
- **Malacoplakia**
  - Associated w/ chronic bacterial infection (eg. immunosuppressed)
  - Yellow plaques with foamy macrophages, multinucleated giant cells, Michelis-Gutmann bodies (dark blue staining mineralized concentrations)
  - PAS-positive material
- **Interstitial cystitis**
  - Chronic autoimmune cystitis (women)
  - Suprapubic pain, dysurea, urgency w/o infection
  - All layers of the bladder wall demonstrate fibrosis, inflammatory infiltrate with mast cells
  - Hunner ulcers

Acute cystitis

- 85% Gram – , usually from fecal flora
- *E. coli* > *Proteus* > *Klebsiella* > *Enterobacter*
- *Staph. Saprophyticus* also common in women
- Associated with catheters, immunosuppression, obstruction/stasis (eg.BPH)
- Other causes:
  - Schistosomiasis (Middle East)
  - Candida, Cryptococcus (long-term antibiotics)
  - Chlamydia, Mycoplasma, Ureaplasma (non-gonococcal urethritis)

Lower Urinary Tract Neoplasms

- **Transitional Cell Carcinoma (90% of bladder cancer):**
  - Can occur in renal calyces, renal pelvis, ureters, or bladder
  - Male to female ratio of 3:1, most at age 50-80, urban>rural
  - Associated w/ cigarette smoking, B-naphthylamine & other aniline dyes, long-term cyclophosphamide therapy, & long-term analgesic use (phenacetin abuse → TCC of renal pelvis)
  - Presentation: painless hematuria, obstruction (hydronephrosis, pyelonephritis)
  - Often multifocal at presentation
  - Tendency to spread by local invasion to adjacent structures, or may metastasize to liver, lungs, bone
  - Recurrence or new growth after excision is common

- **Transitional Cell Carcinoma (continued):**
  - Low grade: deletion of 9p/9q, loss of tumor suppressor gene
  - High grade: deletion of 13q/17p, mutations of p53 gene on 17p
  - Staging (extent of invasion at time of diagnosis) is most important factor in determining prognosis
    - depth of invasion: lamina propria, muscularis propria, microscopic extra-vesicular, gross extra-vesicular, invasion of adjacent structures
    - Once muscularis propria invasion occurs → 50% 5-year mortality rate
  - Noninvasive papillary urothelial carcinoma - papillary growth lined by transitional epithelium with mild nuclear atypia and pleomorphism
  - Noninvasive flat urothelial carcinoma (called carcinoma in situ - CIS) - cytologically atypical malignant cells within a flat urothelium
Lower Urinary Tract Neoplasms

• Squamous cell carcinomas (3-7% of bladder cancer):
  – Chronic irritation or chronic infection → squamous metaplasia
  – \textit{Schistosomiasis hematobium} infection
  – Most aggressive and lethal form
• Adenocarcinomas (rare):
  – Associated w/ urachal remnants, bladder extrophy & extensive intestinal metaplasia, histologically identical to GI adenocarcinoma
  – Signet-ring carcinomas - a rare & highly malignant variant
• Benign leiomyomas and malignant sarcomas (rare):
  – In kids – embryonal rhabdomyosarcoma (ex sarcoma botryoides)
  – In adults – leiomyosarcoma

Prostatitis

• Young to middle-aged men
• Lower back pain, urinary/sexual dysfunction
• Chronic nonbacterial type most common (90%)
  – Unknown etiology
• Also acute/chronic bacterial type (5-10%)
• Normal-sized, smooth, tender prostate on rectal exam
• WBC’s in prostatic secretions
• May lead to chronic cystitis, epididymitis, infertility

Prostate – BPH (Benign Nodular Hyperplasia)

• Common in men > age 50, rubbery nodular enlargement on digital rectal exam
• \textbf{Not pre-malignant}, but can coexist with prostate cancer
• Symptoms: urgency, hesitancy, frequency, nocturia, dysuria
  – complications of urinary retention include UTI, cystitis, & hydrenephrosis
• \textbf{Hyperplasia} of both glandular epithelium and fibromuscular stroma – compresses urethral lumen into vertical slit
  – Found in \textit{periurethral and transitional zones} of prostate (inner zones)
• Increased Free fraction of prostate specific antigen (PSA)
• Dihydrotestosterone (DHT) level is the major trophic factor
  – Finasteride therapy inhibits 5a-reductase, lowers DHT & shrinks prostate

Prostate – Adenocarcinoma

• Also in men > age 50 (most common cancer of older men) increases w/ age, hard irregular nodule on digital rectal exam
• Increased \textbf{Total PSA} w/ decreased Free PSA and increased complexed PSA suggests malignancy
  – in BPH, Free PSA is increased in proportion to Total PSA
• Spread by direct local invasion and through blood & lymph
  – Local extension to seminal vesicles & bladder
  – Metastasis to obturator nodes and pelvic nodes via lymph
  – Metastasis to bone via blood
• \textbf{Osteoblastic} metastasis to lumbar spine (most common sites are axial skeleton, proximal femur & pelvis)
  – Alkaline phosphatase is elevated w/ bone metastasis from prostate

Prostate – Adenocarcinoma cont’d

• Found in \textit{posterior and peripheral zones} (away from urethra)
• Histology shows well defined glandular patterns
  – smaller and more crowded than benign glands, lined by single uniform layer of cuboidal or low columnar epithelium, absent outer layer of basal cells, enlarged nuclei w/ prominent nucleoli
  – perineural invasion often present
• \textbf{Gleason Grade} – used to predict indolent vs aggressive course
  – based on glandular patterns and degree of differentiation - 5 grades
  – Score = sum of two grades, dominant pattern plus secondary pattern
  \begin{align*}
  2 &= \text{most differentiated, 1+1 and 10 = least differentiated, 5+5}
\end{align*}
• Androgens believed to play role in pathogenesis
  – Disseminated cancer may respond to endocrine therapy

Cryptorchidism

• Undescended testicle (one or both)
• No spermatogenesis occurs because of ↑ in temp within the body
• Associated with testicular atrophy and sterility
• Associated w/↑ risk of germ cell tumors, especially seminoma and embryonal carcinoma
  – Risk of germ cell tumors remains high, even after surgical correction
Testicular Torsion (a.k.a. torsion of the spermatic chord)

- In torsion – spermatic chord twists – blood supply cut off
- Most men's testicles are attached posteriorly to scrotum by the mesochornium
  - Without mesochornium, testicle is free floating in the tunica vaginalis
  - Free to twist, allows for torsion
- Called the “bell clapper” deformity – predisposes for torsion
  - Other risk factors – adolescence, strenuous physical activity
- Testicle will take on a bluish-black color
- Testicle will be drawn up into the inguinal canal
  - Due to shortening of the spermatic chord from torsion
- Cremasteric reflex will be absent
- VERY PAINFUL – surgery is imperative to save the testicle

Penile Pathology

- Congenital:
  - hypospadias (open on ventral surface), epispadias (open on dorsal surface); both assoc w/failed testes descent/other malform., predispose to infections
  - phimosis: inflammatory scarring of prepuce causes the opening to be too small to retract; may cause secondary infection/neoplasim
  - paraphimosis: constriction of glans penis after forced retraction of phimotic prepuce; causes urine retention

Penile Pathology

- Infectious:
  - balanoposthitis: infection of glans penis/prepuce; assoc w/ phimosis
  - HPV
- Neoplasms:
  - condyloma acuminatum: benign wart (HPV 6/11); red, papillary;
  - carcinoma in situ aka Bowen's disease: plaque-like lesions with cellular atypia; no BM penetration; precancerous (HPV 16, 18)
  - squamous cell carcinoma: begins on glans penis/inner prepuce; starts as plaque Æ papilla; slow-growing; invasive (HPV 16, 18)

Pituitary Adenomas

- 10% of intracranial neoplasms, peak incidence 30's-50's
- Microadenoma < 1cm, Macroadenoma > 1cm
- Soft, well-circumscribed lesions; larger lesions may compress optic chiasm; 30% non-encapsulated and infiltrate adjacent bone, dura; functional status not reliably predicted by histological appearance
- Relatively uniform, polygonal cells arrayed in sheets or cords, connective tissue is sparse
- May produce over activity of overproduced hormones or loss of activity of other hormones due to secondary destruction of normal cells

Pituitary Adenomas

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Histological Characteristics</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactinomas (30% most common)</td>
<td>Hyperprolactinemia Æ amenorrhea, galactorrhea, loss of libido, infertility</td>
<td>Hyperprolactinemia: amenorrhea, galactorrhea, loss of libido, infertility</td>
</tr>
<tr>
<td>Growth Hormone Adenomas 2nd most common</td>
<td>Children Æ Gigantism, Adults Æ Acromegaly, (tumors may become large)</td>
<td>Children Æ Gigantism, Adults Æ Acromegaly, (tumors may become large)</td>
</tr>
<tr>
<td>Corticotroph Cell Adenoma</td>
<td>Cushing's Disease</td>
<td>Cushing's Disease</td>
</tr>
<tr>
<td>Gonadotroph Cell Adenoma (10-15%)</td>
<td>Secretes hormones inefficiently and variably; LH deficiency = decreased libido in men, amenorrhea in women; usually found due to enlarged size and neurologic complication</td>
<td>Secretes hormones inefficiently and variably; LH deficiency = decreased libido in men, amenorrhea in women; usually found due to enlarged size and neurologic complication</td>
</tr>
<tr>
<td>Thyrotroph Cell Adenoma (1%)</td>
<td>Hyperthyroidism</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Mixed Cell Adenomas</td>
<td>May be mixed population of cells or single population with mixed hormones</td>
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</tr>
<tr>
<td>Non-functional Adenomas (20%)</td>
<td>Numerous mitochondria, infrequent secretory granules, present with mass effect or hypopituitarism</td>
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</tr>
</tbody>
</table>

Panhypopituitarism

- > 75% loss of pituitary parenchyma
- Causes
  - Tumors: pituitary adenoma, craniopharyngioma, etc.
  - Rathke cleft cyst: ciliated cuboidal ep. w/ goblet cells, proteinaceous fluid
  - Ischemic necrosis: Sheehan syndrome (postpartum) most common
  - Empty sella syndrome: secondary to adenoma or infarction
    - Primary form usually not associated with hypopituitarism
    - Hypothalamic lesions: neoplastic, infectious, autoimmune
- Effects
  - Reduced function of thyroid, adrenal cortex, and gonads
  - Pallor (decreased melanocyte stimulating hormone)
**Diabetes insipidus**
- Underproduction of ADH → free water loss
- Causes: head trauma, neoplasms, surgery, idiopathic
- Symptoms:
  - Polyuria, polydipsia, dehydration
  - Brain shrinkage: somnolence, coma, death
  - Serum > 320-330 mOsm acutely w/ possible hyponatremia
- Diagnosis: Rule out diabetes, renal disease first
- Treatment:
  - Fluid replacement w/ normal saline
  - Rapid correction is dangerous

**SIADH**
- Overproduction of ADH → increased water retention
- Causes: small cell lung carcinoma, other ADH-secreting tumors, lung disease, surgery, trauma, medications
- Symptoms:
  - Continued natriuresis in the face of hyponatremia
  - Increased total body water, but NO EDEMA
  - Cerebral edema: lethargy, weakness, seizures, coma, death
  - Dependent on rate of hyponatremia development
- Treatment:
  - Free water restriction and salt intake
  - Lithium carbonate or demeclocycline: ADH antagonists
  - If life threatening: hypertonic saline controlled to 125 mEq

**Hashimoto’s Thyroiditis**
- Chronic autoimmune hypothyroidism
  - middle aged women
- Thyrotoxicosis may occur at onset T-cell mediated + Antibodies against: thyroglobulin, thyroid peroxidase
- TWO types
  1. Goitrous (most common): lymphocytic infiltrate and germinal center formation
  2. Atrophic: gland fibrosis
- Hurthle Cells: abundant eosinophilic granules
- Increased risk of lymphoma

**Painless Subacute Lymphocytic Thyroiditis**
- Subacute (6-8 weeks) autoimmune hyperthyroidism
- Post-partum women
- Antibodies against: thyroglobulin and thyroperoxidase
- PAI N E L S G O I T E R (vs. subacute viral) containing lymphocytes but no germinal centers (vs. Hashimotos)
- 50% progress to Chronic Lymphocytic thyroiditis (Hashimotos)

**Grave’s Disease**
- Autoimmune hyperthyroidism
- TSH receptor- stimulating antibodies (IgG)
- Palpable, diffuse GOITER
  - Hypertrophy and hyperplasia
  - Diminished colloid
  - Some lymphocytic infiltrate
  - Inc. blood flow causes AUDIBLE BRUIT
- Exophthalmos
  - Infiltrate & inc. GAG synthesis & EDEMA
- Pretibial myxedema
- TX: b-blockers, PTU, radiation, surgery

**Hypothyroidism & Hyperthyroidism**
- Hyperthyroidism
  - most common cause is Grave’s disease
  - Common signs and symptoms include weight loss despite increased appetite, diarrhea, heat intolerance
  - Serum TSH low, T3 and T4 elevated
  - Medical emergency: thyroid storm
- Hypothyroidism
  - most common cause is Hashimoto’s disease
  - Common signs and symptoms include slight weight gain (not obese), constipation, cold intolerance
  - Serum TSH high, T3, and T4 are low
  - Medical emergency: myxedema coma.
### Goiter and Multinodular Goiter

- **Diffuse, non-toxic, simple goiter**
  - characterized by thyroid enlargement with excess colloid and absence of nodules
  - may be endemic (iodine deficiency) or sporadic.
  - It results from absolute or relative deficiency of thyroid hormone.
- **Multinodular goiter may be toxic or non-toxic.**
  - TMG and NMG have similar pathogenesis, a combination of environmental and genetic factors.
  - TMG characterized by one or more functional, TSH-independent nodules.
  - TMG may cause subclinical hyperthyroidism or a mild thyrotoxicosis.

### Thyroid Adenomas

- **Benign, solitary, “Cold”, discrete masses**
- Encapsulated with follicular epithelium
- Constitutive activation of TSH receptor signaling to increase cAMP
- Uniform appearing follicles with colloid

### Papillary Thyroid Carcinoma

- Most common thyroid cancer (75-85%)
- Papillae of fibrovascular stalk covered with cuboidal epithelium
- Orphan Annie nuclei—“ground glass” empty looking nuclei with finely dispersed chromatin
- Psammoma bodies—calcifications within papillae
- present as multifocal cold nodule-decrease in hormone synthesis
- Assoc w/radiation exposure
- Good prognosis; 10 yr survival >90%
- METS: cervical nodes (lymphotogenous), lungs

### Follicular Thyroid Carcinoma

- 10-20% of all thyroid cancers (2nd most common after papillary)
- Most common single, encapsulated, COLD nodule with uniform small follicles with colloid
- Hurthle cells: cells with granular, eosinophilic cytoplasm
- Invades hematogenously to bone, lung, and liver
- Associated with iodine deficiency goiter
- Indistinguishable from follicular adenoma on FNA

### Medullary Thyroid Carcinoma

- 5% of thyroid cancers
- neurosecretory tumor of parafollicular or C cells
- produces calcitonin (tumor marker) is converted into amyloid (amyloidosis is key pathologic feature)
- associated with MEN II and III
- polygonal or spindle shaped cells form nests, trabeculae or follicles
- can present with paraneoplastic syndrome (pheochromocytoma)
- 5 year survival of 50%

### Anaplastic Thyroid Carcinoma

- <5% of all thyroid ca
- Undifferentiated in older patients
- Multinodular, aggressive, uniformly fatal
- Hx of Follicular Cancer
- See regional invasion and distant metastasis
**De Quervain's Painful Subacute Granulomatous Thyroiditis**

- Post-viral hyperthyroidism (2-6 wks) → subacute (6-8 wks) hypothyroidism → complete recovery
- F > M, 30-50 yr. old
- Sudden or gradual onset thyroid enlargement and PAIN with fever, malaise, anorexia, myalgia
- T-cell mediated microabscesses → granulomas and giant cells → minor fibrosis

**MEN Syndromes**

- **MEN – Autosomal Dominant**
  - MEN I – three p’s: pituitary, parathyroid, and pancreas
    - Presents with kidney stones and stomach ulcers
  - MEN II – medullary carcinoma of the thyroid PLUS
    - IIA – MCT; Parathyroid hyperplasia; Pheochromocytoma (Sipple Syndrome)
      - IIB or III – similar to IIA, but distinct oncogenic mutation; also accompanied by neuromas or paragangliomas of the skin, oral mucosa, eyes, respiratory tract, GI tract
      - Familial medullary thyroid cancer; II and III associated with ret gene

**Primary Hyperparathyroidism**

- Most common cause of nonmalignant hypercalcemia
- Most commonly occurs in Females > 50 years of age
- Associated with MEN1 and MEN IIa
- **Causes:**
  - Adenoma (85%), sheets of chief cells with no intervening adipose; remainder of the gland (as well as other 3 parathyroids) will be atrophied. Most commonly involves right inferior parathyroid
  - Primary Hyperplasia - All four glands are involved
- **Laboratory findings:**
  - Both serum PTH and serum Ca2+ are increased (abnormal)
  - Chloride:Phosphorus ratio >33

**Primary Hyperparathyroidism**

- Clinical Findings
  - Most commonly present with calcium stones of the kidney
  - Nephrons can calcify leading to polyuria and renal failure
  - Peptic ulcers are seen because Ca²⁺ stimulates gastrin which increases HCL
  - Acute pancreatitis due to activation of phospholipase by Ca²⁺
  - Osteitis Fibrosa Cystica- cystic bone lesions due to increased osteoclast activity, commonly seen in the jaw. Cause a “salt and pepper” appearance of skull on Xray
  - Diagnose with Technetium-99m radionucleotide scan
  - Treatment is surgical removal of adenoma

**Hypercalcemia/Hypocalcemia**

- **Hypercalcemia**
  - Sx: fatigue, N/V, metastatic calcification, renal stones, short QT, wide T wave
  - Causes: HyperPTH (Squamous cell Ca of Lung, parathyroidoma), HCT use (high reabsorption), hyperVitaminD (high GI absorption), bone lysis (multiple myeloma, Paget’s disease)
- **Hypocalcemia**
  - Sx: Tetany (Trousseau & Chvostek), spasticity, long QT
  - Causes: low PTH/VitD, defective VitD activation (liver/renal failure), HypoMg

**Adrenal Pathology**

- ACTH levels cause adrenal cortex:
  - **Hyperplasia:** pituitary or paraneoplastic ACTH-secreting tumors, 21-hydroxylase deficiency
  - **Atrophy:** exogenous steroids, adrenal cortical adenoma (rest of gland shrinks), 2° adrenocortical insufficiency (which is defined as low ACTH)
  - Note that adrenal can be small also from autoimmune destruction (Addison’s) or large from metastatic tumors
  - Adrenal medulla: only pathology is pheochromocytoma
Adrenal Pathology

- Unilateral vs bilateral
- Yellow coloring
- Medullary metastasis and hemorrhage

Adrenal - Cushing’s Syndrome

- *Hypercortisolism w/ 4 main causes (iatrogenic, pituitary, adrenal, ectopic)
- Iatrogenic (most common): corticosteroid tx (long term)
  - zona fasciculate (F) / reticularis (R) atrophy b/c ↓ ACTH secretion from ant. pituitary
  - NO androgen excess
- Pit. tumor: Cushing’s DI – benign ant. tumor secreting ACTH → zona F/R hyperplasia (excess cortisol/androgen)
- Adrenal: tumor producing ↑ cortisol (most are monoclonal, benign)

Adrenal - Cushing’s Syndrome cont.

- Ectopic Cushing’s
  - any non-pituitary Ca secreting ACTH
  - → most common: small cell Ca of lung (also bronchial carcinoid, thymoma)
  - neither low nor high dose dexamethasone can suppress cortisol (ACTH levels are ↑↑↑)
- Dx test= 24h urine free cortisol (*gold standard)
- *Sx: weight gain in adipose areas (moon facies & buffalo hump), muscle wasting as aa are shunted to gluconeogenesis, purple abdominal stria, osteoporosis, DM, hirsutism, HTN, psychological disturbances

Hyperaldosteronism

- Primary Aldosteronism
  - Autonomous overproduction of aldosterone due to:
    - Aldosterone secreting adenoma (Conn’s Syndrome)
      - Solitary, well-circumscribed lesions that are bright yellow on cut section
      - Lipid-laden cortical cells
      - Some nuclear and cellular pleomorphism; no anaplasia
      - Dx important because HTN can be cured surgically
    - Primary adrenocortical hyperplasia
      - Bilateral nodular hyperplasia of adrenal glands
      - Na+ retention, K+ excretion → HTN, hypokalemia
      - (-) feedback of renin-angiotensin system → Plasma renin

Hyperaldosteronism continued

- Secondary aldosteronism
  - Activation of renin-angiotensin system by:
    - Decreased renal perfusion
      - Nephrosclerosis, renal artery stenosis
    - Arterial hypovolemia and edema
      - CHF, cirrhosis, nephrotic syndrome
    - Pregnancy
      - estrogen induced renin increase
    - Increased levels of plasma renin

Adrenogenital Syndromes

- Congenital adrenal hyperplasia
  - Most commonly due to 21-hydroxylase deficiency
    - ↓ aldosterone, ↑ cortisol, ↑ androgens, ↑ ACTH
  - Salt-wasting syndrome w/ complete lack of enzyme
    - Hypotension, hypertension, cardiovascular collapse
    - Male=precocious puberty in boys, oligospermia in older males
    - Female=ambiguous genitalia in infants, virilization in girls/women
  - Simple virilizing adrenogenital syndrome w/ partial lack of enzyme
    - Morphology: bilaterally hyperplastic adrenals; brown cortex due to depletion of lipid
  - Adrenocortical neoplasms
    - Androgen secreting adrenal carcinoma
Adrenal Insufficiency

- **Primary acute** adrenocortical insufficiency
  - Acute stressor in patient with chronic insufficiency
  - Rapid withdrawal of exogenous corticosteroids
  - Adrenal hemorrhage
    - Vulnerable populations include: newborns, postsurgical patients with DIC, anticoagulated patients
    - Waterhouse-Friderichsen syndrome
      - Most often due to *Neisseria meningitidis* septicemia
      - Rapid adrenocortical insufficiency with massive bilateral adrenal hemorrhage
      - Adrenals converted to sacs of clotted blood
      - Hypotension, hyponatremia, hyperkalemia

Adrenal Insufficiency continued

- **Primary chronic** adrenocortical insufficiency (Addison Disease)
  - Autoimmune adrenalitis
    - Scattered residual cortical cells in a collapsed network of connective tissue
  - Variable lymphoid infiltrate
    - Infections: TB, histoplasmosis, coccidioides, AIDS related (CMV)
  - Granulomatous inflammatory reaction with effaced architecture
    - Metastatic cancers: lung, breast, GI, melanoma, hematopoietic
  - Normal architecture obscured by infiltrating neoplasm
    - Progressive destruction of cortex; 90% destroyed before sx evident
    - Increased ACTH \( \rightarrow \) hyperpigmentation
    - Decreased aldosterone \( \rightarrow \) Hyponatremia, hyperkalemia, volume depletion, hypotension
    - Decreased cortisol \( \rightarrow \) hypoglycemia

Adrenal Medulla Tumors

- **Pheochromocytoma**
  - Sporadic (90%) or associated with MEN syndrome (10%)
  - Adrenal medulla or extra-adrenal paraganglia (paraganglioma)
  - Synthesize and release catecholamines (Epi, NE, dopamine)
    - ↑ blood pressure, tachycardia, palpitations, tremor which can be precipitated by stress, exercise, changes in posture, palpation of tumor
    - Complications: catecholamine cardiomyopathy and precipitation of CHF, pulmonary edema, MI, ventricular fibrillation, or CVA

Adrenal Medulla Tumors

- **Neuroblastoma**
  - Malignant tumor of neural crest cells in *kids*; N-myc oncogene
  - Adrenal medulla, sympathetic chain (midline), brain
  - 90% make catecholamines (dx similar to pheochromocytoma)
  - Sx: abdominal mass, fever, weight loss, HTN rarely
**Adrenal Medulla Tumors**

- **Neuroblastoma**
  - Morphology
  - fibrous pseudocapsule or infiltrative
  - necrosis; hemorrhage
  - cells w/ dark nuclei and scant cytoplasm growing in solid sheet
  - Rosettes
  - secretory granules
  - Metastasize to liver, lungs, bone marrow, bones, skin
  - Prognosis largely determined by age and stage but a variety of gene abnormalities also contribute to outcome

**Type 1 Diabetes Mellitus**

- Usually manifests early (<30); accounts for 10% of cases
- Hyperglycemia due to autoimmune destruction of pancreatic β-cells and resultant failure of insulin synthesis
  - T lymphocytes reacting against poorly defined β-cell antigens
  - Weak genetic predisposition but associated with HLA-DR3/DR4
  - Also associated w/ environmental factors (geographic, viral, toxins)
- Plasma insulin levels ↓; require insulin therapy for survival
- Ketoacidosis more common with type 1 diabetes
- Pancreas morphology: ↓ in number/size of islets; prominent lymphocytic infiltrate (insulitis)

**Type 2 Diabetes Mellitus**

- Often manifests later (>40); accounts for 80-90% of cases
- Hyperglycemia due to ↓ responsiveness of peripheral tissues to insulin followed by worsening β-cell dysfunction
  - Genetic factors more important than type 1 but no HLA associations
  - Environmental factors: obesity, sedentary lifestyle, dietary habits
- Plasma insulin concentration is normal or often increased until late in the disease due to β-cell burnout
- Ketoacidosis is much less common
- Pancreas morphology: subtle reduction in islet cell mass; amyloid replacement of islets; fibrosis in later stages

**Non-enzymatic glycosylation in Diabetes**

- Glucose binds to proteins on cell surfaces via ketoamine linkages
  - Amount of glycosylation directly related to degree of hyperglycemia
  - Glycosylated RBC’s (A1c) can be measured to dx DM
  - Rearrange to form Advanced Glycosylated Endproducts (AGE’s) that crosslink and bind to cell surface receptors of endothelium, monocytes, macrophages, lymphocytes, and mesangial cells
    - Cause chemotaxis, cytokine release, vascular leakage, thrombosis, increased synthesis of ECM, entrapment of LDL in vessel walls
    - Complications: Atherosclerosis, CAD, stroke, microvascular injury (neuropathy, nephropathy, retinopathy)

**Small Vessel Disease of Diabetes Mellitus**

- Diabetes is a vascular disease
- Diffuse thickening of vessel basement membrane due to nonenzymatic glycosylation & disturbances of polyl pathways
- Capillaries become leaky
- Microangiopathy leads to diabetic nephropathy, retinopathy, and neuropathy
  - Renal: hyaline arteriolosclerosis of both afferent and efferent vessels
  - Retina: microaneurysms, macular edema, hemorrhagic exudates, intraretinal angio genesis (proliferative diabetic retinopathy), retinal detachment, glaucoma, blindness
  - Neuropathy: vasa nervorum
  - Arteriosclerosis leading to hypertension

**Large Vessel Disease of Diabetes Mellitus**

- Accelerated atherosclerosis involving aorta and medium-large sized arteries
- Can result in:
  - CAD (increase incidence of myocardial infarction)
  - Peripheral vascular insufficiency → gangrene of lower extremities
  - Cerebrovascular disease (ischemic strokes)
  - Renal artery stenosis
Osmotic Damage and Infection in DM

- Osmotic damage occurs in insulin independent tissues:
  - Retina, kidney, and neurons
- Mechanism of osmotic damage:
  - Hyperglycemic state results in \( \uparrow \) uptake of glucose in these tissues and subsequent conversion to sorbitol
  - Sorbitol draws water into cells and creates osmotic damage
- Results of osmotic damage:
  - Cataracts
  - Peripheral neuropathy (motor, sensory, and autonomic degeneration)
- Increased propensity for infections
  - Skin (furuncles, abscesses, gangrene), pneumonia, pyelonephritis
  - Fungal (Candida and \textit{Mucormycosis}), TB, bacterial
Pathology Review Flash Cards for Revision
Neuro, Derm, Bone, Fem Gen
Spring 2009

Neuro - Tissue Reactions

• Anoxia
  – Neurons most sensitive to anoxia reside in the hippocampus, Purkinje cells, and larger neocrotical neurons
  – Affect watershed areas first
  – “red” shrunken neurons
• Decreased consciousness can result from diffuse axonal injury in absence of localizing findings with trauma
  – Due to stretching and tearing of axons
• Primary reaction to injury – edema
  – Return of function related to resolution of edema
• Liquefactive necrosis

Bacterial Meningitis

• Suppurative involvement of the meninges
  – Located in subarachnoid space; communicates with CSF
• Hematogenous dissemination
  – No complement in CSF
• CSF
  – Increased protein, decreased glucose
  – PMNs
  – Gram stain – bacteria
  – Positive culture
• Clinical features
  – Headache, fever
  – Nuchal rigidity, Kernig’s sign
  – Focal neurological deficits
  – Increased intracranial pressure

Viral meningitis

– “aseptic meningitis”
  • Slight increase protein, no decrease in glucose
  • Lymphocytes
• Echovirus, mosquito-borne viruses (west nile virus, eastern equine virus)

Brain Abscess

– “ring” enhancement of abscess
  • Central area of low density, & surrounding area of low density due to edema
  • Fibrosis around abscess
  • CSF – increased protein, few cells

Other Infections

• Viral meningitis
  – “aseptic meningitis”
  • Slight increase protein, no decrease in glucose
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Brain Abscess

– “ring” enhancement of abscess
  • Central area of low density, & surrounding area of low density due to edema
  • Fibrosis around abscess
  • CSF – increased protein, few cells

Syphilis

• Meningovasculitis
  – Infiltration of meninges and vessels by lymphocytes and plasma cells; may cause symptoms of meningitis or vascular occlusion.
• General Paresis
  – Atrophy, loss of cortical neurons especially in frontal lobes, gliosis, proliferation of microglial cells (rod cells), perivascular lymphocytes and plasma cells.
• Tabes Dorsalis
  – Inflammatory lesions involving dorsal nerve roots. Loss of axons and myelin in dorsal roots with Wallerian degeneration of dorsal columns. (T. pallidum is absent in cord parenchyma.)
### Encephalitis

- **Viruses**
  - Headache, fever, seizure, altered consciousness
  - Increased intracranial pressures, no other CSF findings
  - Neonates and immunosuppressed – herpes, cytomegalovirus, HIV
  - Adults – vector-borne infections (West Nile, eastern equine, etc.); polio
  - Most hematogenous
  - Spread along nerves: rabies, herpes simplex

- **Pathology**
  - Perivascular cuffing by lymphocytes and plasma cells;
  - Neuronal necrosis;
  - Inclusion bodies;
  - Microglial proliferation and glial nodules;
  - Hemorrhagic necrosis
  - Rod cells: reactive microglial cells

### Specific Pathologic Findings

- **Herpes**
  - Necrosis and hemorrhages in temporal lobe

- **Cytomegalovirus**
  - Owl’s eye nuclear inclusions; cytoplasmic inclusions
  - Periventricular necrosis, focal calcifications

- **Rabies**
  - Negri bodies in Purkinje cells of cerebellum

### HIV

- **Immunosuppression**
  - Cryptococcus (India ink preparation) – mononuclear, normal protein, normal glucose
  - Herpes, cytomegalovirus, toxoplasmosis, PML

- **AIDS-Dementia Complex**
  - Cognitive, motor, and behavioral dysfunction. The symptoms are due to subcortical lesions, with microscopic changes mainly in basal ganglia, thalamus and subcortical white matter
  - HIV antigen is found in microglia, macrophages and multinucleated giant cells (formed by fusion of macrophages)
  - Microscopic changes include: foci of necrosis, gliosis, and/or demyelination, microglial nodules, multinucleate cells

### Progressive Multifocal Leukoencephalopathy

- More common in immunosuppressed
- Intellectual deterioration and dementia over months
- JC papovavirus
- Multiple (multifocal) areas of demyelination in the white matter
- Little, if any, inflammatory reaction
- Inclusion bodies found in oligodendrocyte nuclei, large astrocytes with bizarre nuclei

### Subacute Sclerosing Panencephalitis

- Rare disease of children and adolescents
- Associated with a defective measles virus (myxovirus)
- Personality changes, intellectual decline progressing to dementia. The course is progressive deterioration, with a duration of 1 month to several years.
- Changes involve both white matter and gray matter with cortical atrophy and demyelination.
- Oligodendrocytes and neurons contain inclusion bodies

### Spongiform Encephalopathy

- **Creutzfeldt-Jakob Disease**
  - 40 and 80 years of age
  - Sporadic; transmission has occurred by corneal transplant or administration of contaminated growth hormone
  - Dementia and myoclonus
  - Deterioration, with death occurring usually in 3-12 months
  - Routine CSF findings are usually normal
  - Spongiform encephalopathy in gray matter throughout brain and spinal cord
- Kuru - cannibalism
- "Mad Cow" Disease – new variant CJD
Toxicities

- Alcohol
  - Associated with petechial hemorrhages and gliosis of the mamillary bodies, discoloration of structures (hemosiderosis) surrounding the third ventricle, aqueduct, and fourth ventricle
  - Toxic vs. nutritional; Deficiency of thiamine

- Peripheral neuropathy
  - Bilateral limb numbness, tingling, and paresthesia
  - Alcoholic cerebellar degeneration; ataxia, wide-based gait; cerebellar vermic atrophy
  - Cognitive problems and dementia
  - Psychiatric: anxiety, hallucinations, paranoid delusions

- Korsakoff’s psychosis
  - Anterograde amnesia and milder retrograde amnesia; impairment in visuo-spatial, abstract, and conceptual reasoning; confabulation; responds variably to thiamine replacement

- Wernicke’s syndrome
  - Sixth nerves palsy and ataxia; nystagmus
  - Clinical triad: ophthalmoplegia, ataxia, and global confusion
  - Disoriented, indifferent, and inattentive; ocular nystagmus on lateral gaze; lateral rectus palsy (usually bilateral); conjugate gaze palsies, and ptosis
  - Ataxia improves more slowly than the ocular motor anomalies

Systemic Diseases

- Liver failure (alcoholic cirrhosis): hyperammonemia – asterixis
- Uremia: symmetric, peripheral neuropathy
- Diabetes: bilateral symmetrical neuropathy
- Autonomic instability
- Nutritional
  - Subacute combined degeneration – Vitamin B12
    - Generalized weakness and paresthesias; loss of vibration and position sense; motor defects limited to legs; mental symptoms include irritability, apathy, somnolence, suspiciousness, confusional psychosis, and intellectual deterioration
  - Follic acid deficiency: developmental abnormalities, especially closure of neural tube

Trauma – Intracranial Hemorrhages

- Epidural hematoma
  - Middle meningeal artery
  - “Lucid” interval between an initial loss of consciousness and later accumulation of blood
  - Worse prognosis (coma, herniation)
- Subdural hematoma
  - Delayed onset of symptoms – headache and confusion
  - Localized hematoma in association with skull fracture
  - Tearing of bridging veins beneath the dura
- Duret hemorrhages
  - Medial temporal lobe herniation
    - Example: streptococcal meningitis
  - Tearing of branches of basilar artery
  - Hemorrhagic infarcts in the midbrain and pons
  - Ventral-to-dorsal orientation

Hemorrhages

| Tearing of middle meningeal artery | Epidural hematoma |
| Tearing of bridging veins          | Subdural hematoma |
| Tearing of branches of basilar artery | Duret hemorrhages |
| Rupture of berry aneurysm          | Subarachnoid hemorrhages |

Berry Aneurysm

- Congenital weakness of intracerebral artery wall (1 in 100)
- Saccular aneurysm near Circle of Willis
- If ruptures, results in subarachnoid hemorrhage (headache, blood in CSF)
- Rupture when reach 4-7 mm
- Often asymptomatic until rupture
- Associated with other malformations, familial syndromes
  - Autosomal dominant polycystic disease
  - Ehler’s-Danlos syndrome
- Does not result in herniation
Other Hemorrhages

- **germinal matrix hemorrhage**
  - Premature infants
  - Hypoxemia, hypercarbia, acidosis, changes in blood pressure
  - Hemorrhage into germinal matrix
  - Extend into cerebral ventricles (intraventricular hemorrhage)
  - Organization of blood can lead to obstruction of aqueduct of Sylvius and hydrocephalus
- **“coup” injury**
  - Injury to stable head adjacent to site of blow
- **contrecoup injury**
  - Moving head strikes a stable object
  - Force is transmitted to opposite side of the head
  - Backward fall – contusions to inferior frontal lobes, temporal tips, and inferior temporal lobes

Alzheimer’s Disease

- **Progressive dementia with memory loss**
- **Neurofibrillary tangles**
  - Hippocampus, amygdala, neocortex
  - “congophilic angiopathy” – deposition of amyloid in arteriolar media
- **Multiple associations**
  - Formation and aggregation of the Aβ peptide derived from abnormal processing of amyloid precursor protein; cleavage by β-secretase
  - Inheritance of ApoE4 gene
  - Mutations in presenilin genes
- **Cerebral atrophy (hydrocephalus ex vacuo)**

Degenerative Diseases

- **Parkinson’s**
  - Clinical findings
    - Difficulty initiating movement
    - Muscular rigidity
    - Expressionless facies
    - “pill-rolling” tremor
  - Loss of pigmented neurons in substantia nigra
- **Pick’s disease**
  - Similar to Alzheimer’s, but more frontal features and less memory loss
  - “knife-like” gyral atrophy of frontal and temporal lobes; sparing of parietal and occipital lobes
  - Pick bodies – intracytoplasmic, faintly eosinophilic rounded inclusions
  - Stain for tau protein

Degenerative Diseases

- **Huntington’s Chorea**
  - Midlife
  - Autosomal dominant
  - Worsening choreiform movements
  - Behavioral change without memory loss
  - Expansion of CAG repeats on chromosome 4 (huntingtin gene)
  - Atrophy, neuronal loss with gliosis in caudate, putamen, and globus pallidus
- **Dementia with Lewy bodies**
  - Clinical features of Alzheimer’s and idiopathic Parkinson’s
  - Spheroidal, intraneuronal, cytoplasmic, eosinophilic inclusions – stain for α-synuclein

Inherited Degenerative – Children

- **Tay-Sachs**
  - Disease of infancy and childhood
  - Deficiency of hexosaminidase A
- **Metachromatic leukodystrophy**
  - Affect white matter extensively
  - Cause myelin loss and abnormal accumulation of myelin
  - Lysosomal enzyme defects

Multiple Sclerosis

- Lesions separated in time and space
- Central demyelination (oligodendrocytes)
- Progressive with relapses and remissions
- Optic nerve most common presentation
- Oligoclonal immunoglobulins in CSF
- Both motor and sensory
Ischemic Stroke

- Involves thrombotic obstruction of arterial flow
  - Most common: thrombosis of atherosclerotic plaque and downstream ischemia
  - Less common: embolic disease
- Most common: middle cerebral artery
- Primary pathophysiology: advanced atherosclerosis, atherosclerosis of carotids, hypercholesterolemia
  - May be preceded by transient ischemic attacks

Ischemic Stroke

- Involves cortex, aphasia
  - Particularly speech areas
  - Broca – motor
  - Wernicke - receptive
- Contralateral, differential between upper and lower limbs (homunculus)
- Rapidly progressive, may reverse with return of blood flow
- Initial injury: edema which reverses
- Necrosis leads to liquefactive necrosis, atrophy
  - Remote cyst formation

Hemorrhagic stroke

- Hemorrhage in area of internal capsule, putamen,
- Primary pathophysiology: hypertension
- Progression depends on rate and size of bleed
- May result in increased intracranial pressures and herniation
- Contralateral weakness, sensory loss
- Both limbs, distal>proximal
- No aphasia (except motor dysarthria)

Lacunar infarcts

- Hypertension of straight penetrating end arteries of middle cerebral artery
- Hypertension leads to arteriolosclerosis and narrowing of lumen
- Chronic ischemia leads to development of cysts (remember necrosis of brain results in liquefactive necrosis) – lacunae
- Area of internal capsule
- May precede hemorrhagic stroke
- Usually incidental finding

Arteriovenous malformation

- Young to middle aged adults (Senator Tim Johnson)
- Mimic tumor, stroke
- Mass lesion consisting of tortuous vessels
- Frontal lobe – behavior changes, seizures
- May bleed slowly or suddenly
- Gliosis (reaction to slow blood leakage)

Neoplasms

- Neoplasias of glial cells and epithelial linings, not axons or nerves
- Differential
  - Adult vs. children
  - Rate of development (years to weeks)
  - Location (cerebral vs. extracerebral vs. spinal cord)
  - Morphology on CT (diffuse vs. well demarcated)
### Tumor vs. Other

- **Length of development** – subacute
- **Localizing signs and symptoms**
  - Unilateral
  - Specific location – visual, symptoms
  - Seizure activity
- **Primary (solitary) vs. Metastases (multiple)**
  - Intracerebral
  - Tumor emboli settle in vessels in gray-white junction
  - Don’t metastasize outside of cranium; within cranium, spread through arachnoid space

### Adults

- **Meningioma**
  - Most common benign brain tumors
  - 30% of adult brain and CNS tumors
  - Dural (extracerebral) location, growth over months, well-circumscribed, often asymptomatic until large
  - Tumor of arachnoid - elongated cells with pale, oblong nuclei, pink cytoplasm, psammoma bodies

- **Glioblastoma multiforme**
  - 25% of adult tumors (half of glial tumors)
  - Most common intracranial malignant tumor
  - Middle age
  - Rapidly progressive intracerebral growth (weeks to months)
  - Invasive, not circumscribed
  - Necrosis, nuclear pseudopalisading, hyperchromatic cells
    - Perineurotic palisading
    - Glomeruloid vascular proliferation

- **Astrocytomas**
  - Large nuclei, prominent fibers, and negligible mitotic activity

- **Oligodendromas**
  - Intracerebral glial tumors
  - Solitary, well-circumscribed masses
  - Homogeneous cells with dark nuclei, stain with GFAP

- **Oligodendromas vs. astrocytomas**
  - Astrocytomas less well circumscribed
  - Astrocytomas more common

### Other Adult

- **Cerebral lymphoma**
  - HIV patients
  - B-cell large cell lymphoma (CD19, CD20)
- **Ependymomas**
  - Arise in ventricles or spinal canal
  - Rare in adults
    - Myxopapillary variant – more common in adults than children
      - Cuboidal cells around papillary cores in a myxoid background
      - Arise in ventricles
- **Schwannomas**
  - Cerebellopontine angle, eighth nerve

### Children

- **Most commonly occur in posterior fossa**
  - Involve cerebellum – ataxia, gait disturbances
  - Block CSF flow, cause hydrocephalus
- **Astrocytoma – best prognosis**
  - Pilocytic astrocytoma – cystic cerebellar astrocytoma
  - Older children
  - Stain with GFAP, long cellular processes
Children

- Medulloblastoma
  - Peak age 5 years
  - Midline, small blue round cells
  - Homer Wright pseudo-rosettes
  - Poor prognosis

- Ependymoma
  - Older children and adolescents
  - Floor of fourth ventricle
  - Tumor rosettes
  - Poor prognosis

Spinal Cord Tumors

- Intramedullary (10%)
  - Ependymomas
  - Astrocytomas
  - Glioblastomas

- Extramedullary (90%)
  - Schwannomas
  - Neurofibromas
  - Meningiomas

Neurofibromatosis

- Familial syndromes – neurocutaneous syndromes
  - Type I (peripheral)
    - Autosomal dominant
    - Café au lait spots
    - Schwannomas (cranial nerves, peripheral nerves, neurofibromas (intracranial)); may be multiple
    - Plexiform neurofibromas
  - Type II (Central)
    - Autosomal dominant (chromosome 22)
    - Bilateral schwannomas of the eighth nerves or multiple meningiomas

Tuberous Sclerosis

- “phakomatoses” – hamartomas and neoplasms develop throughout the body
- Cutaneous abnormalities
- Cortical tubers – hamartomas of neuronal and glial tissues
- Other features
  - Renal angiomyolipomas, renal cysts
  - Subungual fibromas
  - Cardiac rhabdomyomas

Increased intracranial pressure

- Symptoms
  - Papilledema
  - Cranial nerve dysfunction (bilateral)
  - Increased opening pressure on spinal tap (check for papilledema first!)
  - Progressive evolution of loss of consciousness, herniation

- Hydrocephalus
  - Communicating
  - Non-communicating
  - Hydrocephalus ex-vacuo

Forms of Herniation

- Cingulate gyrus herniation
- Midline shift
- Uncal herniation
- Cerebellar tonsil herniation
- Downward displacement (central herniation)
Developmental Defects

- **Anencephaly**
  - absence of the brain or of all parts except the basal ganglia, brainstem and cerebellum.
  - failure of closure of the anterior neuropore
  - Elevated maternal serum α-fetoprotein

- **Holoprosencephaly**
  - cerebral hemispheres fail to divide properly.
  - associated with trisomy 13-15 and other chromosomal defects
  - total or partial lack of division of telencephalic vesicles, optic vesicles, and/or olfactory vesicles

- **Meningomyelocele**
  - meninges and spinal cord protrude through overlying defect in the vertebral column
  - lumbosacral location.
  - also have hydrocephalus and Arnold-Chiari malformation

- **Encephalocele**
  - meninges and brain tissue protrude through a skull defect.

Spinal Column

- **Spina bifida** - general term for a midline skeletal defect in the spine of any type.
  - Spina bifida occulta - closure defect of posterior vertebral arch; may be associated with overlying dimple, hair
  - Congenital dermal sinus - least serious and most common mid-line defect. Defects range from dimpling of skin over lumbosacral area to sinus tracts in this region.
  - Meningocele - sac containing meninges & CSF protrudes through skeletal defect (rare)
- **Syringomyelia** – cervical vertebrae

Dandy-Walker

- malformation of vermis (anterior vermis displaced rostrally, inferior vermis reduced to abnormal white matter on medial surfaces of hemispheres)
- cystic dilatation of fourth ventricle, with wall of cyst composed of ependyma and leptomeninges
  - lateral displacement of cerebellar hemispheres by 4th ventricle
- increased volume of posterior fossa, with upward displacement of lateral venous sinuses.
- obstruction of foramina of Luschka and Magendie, with production of hydrocephalus

Arnold-Chiari

- Type I (adult type) has variable herniation of cerebellar tonsils and is frequently accompanied by syringomelia
- Type II (infantile type), called the Arnold-Chiari malformation here,
  - polymicrogyria
  - meningomyelocele
  - hydrocephalus
  - beak-shaped colliculi, displacement of the medulla and fourth ventricle down into the cervical segments

Other

- **Central pontine myelinolysis**
  - Too rapid correction or normalization of hyponatremia
  - Osmotic demyelination
  - Results from chronic adaptation to hyponatremia with formation of intracellular osmoles
  - Most often a result of alcoholism
    - Can also occur with rapid normalization of sodium from SIADH
  - Prognosis is poor
Response to Injury - Axons

- **segmental demyelination**
  - Dysfunction of Schwann cell or damage to myelin sheath (no 1st abnormality of axon)
  - Disintegrating myelin engulfed by Schwann cells, later macrophages
  - Denuded axon undergoes remyelination
    - New formed internodes are shorter than normal
    - Several new internodes are required to bridge gap
    - New myelin thinner than original
  - Sequential episodes of demyelination and remyelination leads to concentric skeins and formation of “onion bulbs”

- **axonal degeneration**
  - Implies primary destruction of axon with secondary disintegration of myelin sheath
  - May be due to trauma, ischemia, underlying abnormality of neuron or axon
  - Response to transection: Wallerian degeneration
    - Axon breaks down within one day
    - Schwann cells catabolize myelin and engulf axon fragments
    - Macrophage phagocytosis of axonal and myelin debris
    - Stump (proximal portion) shows degenerative changes in most distal 2 or 3 internodes
    - If neuron remains viable, undergoes regenerative activity

- **symptoms associated with neuronal degeneration**
  - Lower motor neurons: muscular atrophy, fasciculations, weakness
  - Upper motor neurons: hyperreflexia, spasticity, and a Babinski reflex

- **nerve regeneration**
  - Involves growth cone at end of remaining stump
  - Multiple, closely aggregated thinly myelinated small-caliber axons (regenerating cluster)
  - Haphazard growth and mass of tangled fibers - pseudoneuroma
  - Slow rate of axonal transport - growth only 2 mm/day
  - Denervated muscle usually re-innervated by adjacent fibers before original fiber regenerates

Response to Injury - Axons

Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease)

- **Clinical Characteristics**
  - Middle-aged
  - 10% familial; genetic locus Cu/Zn binding superoxide dismutase gene
  - Loss of upper and lower motor neurons
  - Progressive, symmetric muscular weakness
  - May present with bulbar symptoms, with sparing of the extra-ocular muscles
  - Intact mental function; death from respiratory complications

- **Pathology**
  - Gliosis and loss of motor neurons
  - Pallor of lateral corticospinal tracts
  - Neuronal loss in anterior horns of spinal cord
  - Denervation atrophy of muscle fibers

Guillain-Barre Syndrome

- **Clinical Characteristics**
  - Life-threatening diseases of peripheral nervous system
  - Death (2-5%) from respiratory paralysis; recovery over several weeks if respiratory function maintained
  - Acute illness, symmetric, ascending paralysis (distal to proximal)
  - Motor-sensory with loss of deep tendon reflexes
  - Elevation of CSF protein (no white cells)

- **Pathology**
  - 2/3 cases preceded by influenza-like illness
  - Most intense inflammation in spinal and cranial motor roots (anterior roots)
  - Autoimmune segmental demyelination; nerve conduction slowed
  - Thought to be T-cell mediated, but treatable with plasmapheresis

Werndig-Hoffman disease (infantile progressive spinal muscular atrophy)

- “Floppy infant syndrome”: Severe form of lower motor neuron disease which presents in neonatal period
- Death within a few months from respiratory failure or aspiration pneumonia
- Autosomal recessive condition, pathogenesis unknown

- **Morphology**
  - Severe loss of lower motor neurons with profound neurogenic atrophy of muscle
  - Degeneration of motor axons of the anterior roots
### Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

- **Clinical Characteristics**
  - radiculopathy
  - chronic relapsing, remitting course
  - symmetric, mixed sensorimotor polyneuropathy
- **Morphology** - Similar to GB, because of chronic nature, well-developed onion-bulb structures are seen
- Biopsy of sural nerves shows recurrent demyelination and remyelination with **onion bulb structures**
- Clinical remissions with steroid treatment and plasmapheresis

### Infectious Neuropathies

#### Varicella-Zoster (post Chicken Pox)/Shingles
- latent infection of the sensory ganglia of the spinal cord and brain stem
- virus transported along sensory nerves to infect epidermal cells; reactivation vesicles appear distributed along dermatome (very painful!!!)
- reactivation may be related to decreased cell mediated immunity
- affected ganglia show neuronal destruction with abundant mononuclear infiltrates; regional necrosis with hemorrhage

### Hereditary Neuropathies

#### HMSN I (Charcot-Marie-Tooth disease)
- autosomal dominant/most common
- presents in childhood or early adulthood; normal life span; limited disability
- progressive, symmetric muscular atrophy, particularly in the calf muscles (peroneal muscular atrophy)
- suggests Schwann cell abnormality
  - palpable nerve enlargement/hypertrophy: demyelination and remyelination of peroneal nerve
- HMSN II - similar to HMSN I, presents at later age and nerve enlargement is not seen; autosomal dominant
- HMSN III (Dejerine-Sottas disease)
  - AR; present in infancy; delay in acquisition of motor skills
  - slow progression of distal weakness plus truncal weakness
  - enlarged, palpable peripheral nerves, onion bulb formation

### Acquired Metabolic and Toxic Neuropathies

#### Hand/foot (distal) symmetric distribution
- Numbness tingling (primarily sensory)
- diabetes mellitus, alcoholism, uremic neuropathy
- industrial or environmental chemicals - axonal degeneration
  - acrylamide, heavy metals (arsenic, lead), vinca alkaloids (plants, drugs), organophosphates (pesticides)
- tumor-associated syndromes

### Tumor-associated syndromes

- direct infiltration or compression of peripheral nerves (Pancoast’s; cauda equina involvement)
- **Plasma cell dyscrasias** (Two types)
  - Amyloid (light chain deposition) vs. monoclonal IgM gammopathy
  - compression syndromes - similar to carpal tunnel syndrome
- **Paraneoplastic syndromes** - solid tumors
  - most often associated with small cell carcinoma of the lung
  - degeneration of dorsal root ganglion cells with proliferative responses by satellite cells and inflammatory infiltrates
    - plasma cells and lymphocytes, predominantly CD8
    - sensorimotor lesion - weakness and sensory deficits more pronounced in the lower extremities that progress over months to years
  - Eaton-Lambert syndrome

### Schwannomas

- Benign
  - neural crest derived Schwann cells
  - within cranial vault, most common location is the cerebellopontine angle, attached to eighth nerve
  - extradural tumors most commonly found in association with large nerve trunks
- **Malignant schwannoma** (malignant peripheral nerve sheath tumor, MPNST)
  - highly malignant, locally invasive
  - multiple recurrences with eventual metastatic spread
  - never arise from malignant degeneration of benign schwannoma; arise from plexiform neurofibromas (NF-1)
Neurofibroma

• Cutaneous/peripheral nerve form
  – markers of diverse lineages, including Schwann cells, perineurial cells, and fibroblasts
  – Unencapsulated, highly collagenized masses of spindle cells
• Plexiform neurofibroma
  – defining lesion of neurofibromatosis type 1
  – difficult to remove surgically
  – high potential for malignant transformation; frequently multiple

Myasthenia gravis

• Clinical features
  – if before age 40, F>M
  – motor weakness which fluctuates – increases with muscle use
    • exacerbations by intercurrent illness
    • sensory and autonomic functions not affected
  – characteristic temporal and anatomical distribution
    • extracranial muscles commonly involved (ptosis and diplopia)
• Diagnostic features
  – decrement in motor responses with repeated stimulation
  – Tensilon test: transient improvement when administered anticholinesterase agents

Myasthenia gravis

• Decrease in number of muscle acetylcholine receptors secondary to anti-receptor antibodies
  – can be passively transferred to animals
  – circulating anti-AChR causes decrease in receptor number (increased receptor internalization and destruction) and damage to post-synaptic membrane secondary to complement fixation
  – often associated with thymic hyperplasia or thymomas; patients respond to thymectomy
• Morphology
  – muscle biopsies unrevealing; may have diffuse changes with Type 2 atrophy
  – immune complexes present in synaptic cleft
  – thymic hyperplasia with germinal centers

Eaton-Lambert syndrome

• Paraneoplastic syndrome (most commonly small cell carcinoma of the lung)
• Proximal muscle weakness with autonomic dysfunction
• Does not respond to Tensilon test or show increased weakness with repetitive stimulation
• ACh receptors OK, but fewer vesicles are released on synaptic transmission
• Passive transfer of syndrome with IgG

Botulism (Clostridium botulinum)

• Secondary to toxin production in improperly prepared foods or an anaerobic infection
  – No infection with organism; absorption of ingested toxin
  – Neonates: necrotizing intestinal infection by C. botulinum from honey
• Paralysis due to disruption of presynaptic neurotransmitter release

Types of muscle fibers

<table>
<thead>
<tr>
<th>Terms</th>
<th>Characteristics</th>
<th>Function</th>
<th>pH 4.2</th>
<th>pH 9.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Slow type, red type</td>
<td>have many mitochondria, myoglobin, and oxidative enzymes</td>
<td>wt. bearing and sustained force</td>
<td>dark</td>
</tr>
<tr>
<td>Type II</td>
<td>Fast type, white type</td>
<td>rich in glycolytic enzymes</td>
<td>rapid, purposeful movement</td>
<td>light</td>
</tr>
</tbody>
</table>

• Determinant of muscle fiber type - determined by the motor neuron that innervates it (i.e., if the neuron type changes, the muscle type will change along with it); staining for ATPase
Response to Injury - Muscle

- **Denervation atrophy** - secondary to axonal loss
  - group atrophy - type group becomes denervated
  - down regulation of myosin and actin synthesis
  - decreased cell size with resorption of myofibrils
  - cytoskeletal reorganization - rounded zone of disorganized fibers (target fiber)
  - type 2 fiber atrophy - inactivity or disuse; also pyramidal tract disorders, neurodegenerative diseases
- **Reinnervation**
  - muscle fibers re-innervated by sprouts from adjacent nerves incorporated into muscle fiber group for that nerve
  - orphaned fibers assumes fiber type of neighbors; leads to type grouping

Response to Injury - Muscle

- **Primary damage to muscle** - segmental necrosis
  - primary reaction of muscle fiber
  - results in myophagocytosis
- **Regeneration**
  - cells recruited from satellite population
  - regenerating cells large, with internalized nuclei; basophilic due to increased RNA content
  - vacuolation; intracytoplasmic deposits with loss of fibers; deposits of collagen, fatty infiltration
- **Hypertrophy** - secondary to increased load
- **Muscle fiber splitting** - invagination of membrane along large fibers, with apparent splitting of fiber

Duchenne’s muscular dystrophy

- **Epidemiology**
  - X-LINKED (1/3500 males)
  - female carriers show increased plasma levels of creatine kinase and mild muscle damage
  - mutations in gene for dystrophin; 1/3 new mutations
- **Clinical Characteristics**
  - most severe of the dystrophies
  - early motor milestones met on time; develop inability to keep up with peers
  - clinically manifest by age of five; wheelchair by 10 or 12
  - weakness begins in pelvic girdle muscles and extends to shoulder; use of arms to get up called “Gower’s maneuver”
  - cognitive impairment to mental retardation

Duchenne’s muscular dystrophy

- **Morphology**
  - degeneration, necrosis, and phagocytosis of muscle fibers
  - variation in muscle fiber size with both small and giant fibers; fiber splitting
  - increased numbers of internalized nuclei (muscle regeneration)
  - replacement of muscle fibers by fatty infiltrate
- **Clinical Findings**
  - serum creatine kinase elevated in first decade; may return to normal as muscle is destroyed
  - enlargement of calf muscles: pseudohypertrophy
  - progressive; death by early 20’s from respiratory insufficiency, lung infection, or cardiac decompensation
  - changes in heart result in heart failure or arrhythmias

Becker’s Muscular Dystrophy

- X-LINKED RECESSIVE
- similar to Duchenne’s, but less common and less severe
- onset later in childhood and into adolescence
- slower, variable rate of progression
- involves changes to, not loss of dystrophin gene locus
- normal life span with rare cardiac involvement

Other

- Facioscapulohumeral muscular dystrophy
  - AUTOSOMAL DOMINANT
  - disease of adolescents-young adults
  - weakness of muscles of face, neck, and shoulder girdle
  - dystrophic myopathy with inflammatory infiltrate
- Limb-girdle dystrophy
  - AUTOSOMAL RECESSIVE/SPORADIC CASES
  - onset as adolescent or young adults
  - weakness of proximal muscles of upper and lower extremities
  - progression variable; variable dystrophic myopathy
Myotonic dystrophy

- Myotonia = sustained involuntary contractions
  - patients c/o stiffness, unable to release grip
  - percussion of thenar eminence elicits myotonia

- Epidemiology/inheritance
  - AUTOSOMAL DOMINANT
  - increasingly severe and at younger age in succeeding generations: ANTICIPATION

- Etiology/Pathogenesis
  - gene for myotonin-protein kinase, unstable mutation
  - damage collects with each generation

Myotonic dystrophy

- Clinical Characteristics
  - late childhood with gait difficulties, foot weakness
  - progresses to involve hand and wrist extensors
  - atrophy of muscles of face (ptosis)
  - cataracts present in nearly every patient
  - also: frontal balding, gonadal atrophy, cardiomyopathy, smooth muscle involvement, decreased plasma IgG, and abnormal glucose tolerance test

- Morphology
  - muscle dystrophy similar to DMD
  - increase in the number of internal nuclei in chains
  - ring fibers
  - relative atrophy of Type I fibers
  - dystrophic changes in muscle spindle fibers (unique)

Congenital Myopathies

- onset in early life, nonprogressive or slowly progressive course, proximal or generalized muscle weakness, hypotonia; "floppy babies" or may have severe joint contractures

- Syndromes
  - Nemaline myopathy
  - Lipid myopathies
  - Mitochondrial myopathies
  - Cradle’s syndrome
  - Pompe’s disease

- Also: ion channel myopathies (periodic paralysis and myotonia associated with hyper-, hypo-, or normokalemia
  - malignant hyperthermia – dramatic hypermetabolic state associated with induction of anesthesia; familial susceptibility

Toxic Myopathies

- thyrotoxic myopathy - proximal muscle weakness, fiber necrosis with regeneration, interstitial lymphocytes; focal myofibril degeneration with fatty infiltrate

- hypothyroidism - cramping and aching of muscles with slowed reflexes and movements; fiber atrophy, internal nuclei, glycogen aggregation, accumulation of mucopolysaccharides (myxedema)

- thyrotoxic periodic paralysis - episodic weakness often accompanied by hypokalemia; M>F, Japanese descent; dilatation of sarcoplasmic reticulum and intermyofibril vacuoles

- alcohol-induced - drinking with RHABDOMYOLYSIS/myoglobinuria; pain generalized or confined to single muscle group; swelling of myocytes with fiber necrosis, myophagocytosis, and regeneration

Loss of Pigment

- Vitiligo
  - Irregular, well-demarced macules devoid of pigment
  - Loss of melanocytes
    - autoimmunity
    - neurohumoral factors
    - toxic melanin synthesis metabolites

- Albinism
  - Congenital absence of pigmentation
    - Multiple abnormalities

Increased Pigmentation

- Freckles (ephilis)
  - Tan-red to brown macules
  - ↑ with sun exposure
  - Normal number of melanocytes
  - ↑ melanin within basal keratinocytes

- Melasma
  - Darkening of skin
  - Under hormonal control (menopause, pregnancy)

- Lentigo
  - Macular (flat), delimited pigmented area
Nevi

• Progression
  – begins as small tan dot; grows as uniformly colored tan-brown area with well-defined, rounded borders
  – after 1-2 decades gradually flattens and returns to normal

• Maturation of Nevi
  – migration of cells into dermis accompanied by process termed “maturation”
  – less mature, more superficial cells are larger, produce more melanin pigment, grow in nests
  – more mature, deeper nevi cells are smaller, produce little or no pigment, grow in cords
  – the lack of maturation in melanomas is a key feature distinguishing melanomas from nevi

• Junctional/Compound/and Dermal forms
  – Cells migrate to dermis on maturation
  – change from dendritic single cells to nests of round to oval cells
  – increase in number of melanocytes in basal epidermal layer with hyperpigmentation
  – form nests at tips of rete ridges
  – migrate into dermis to form cellular lesion
  – dermal components differentiate along lines of Schwann cells
  – core of 20 yr. old nevus composed of neuromesenchyme
  – undergoes fibrosis, flattening, eventual disappearance

Dysplastic Nevi (BK moles)

• Pathogenesis
  – autosomal dominant, familial syndromes associated with hundreds of lesions on body surfaces (both sun exposed and non-exposed areas)
  – may be associated with chromosomal instability
  – most are clinically stable, but may undergo stepwise progression to malignant melanoma

• Pathology
  – larger than usual nevi; flat macules with variegation of pigmentation
  – characterized by abnormal pattern of growth and aberrant differentiation; cytologic atypia
  – focal areas of eccentric melanocytic growth
  – associated with subjacent lymphocytic infiltrate

Seborrheic keratosis

• Clinical features
  – middle aged or older individuals; commonly affect trunk
  – multiple small lesions on face of blacks: dermatosis papulosa nigra
  – sign of Leser-Trelat: paraneoplastic syndrome

• Pathologic features
  – well-demarcated, flat, coin like plaques mm-cm
  – uniformly tan to dark brown
  – velvety to granular surface
  – trabecular arrangement of sheets of basilar cells with keratin pearls
  – pores impacted with keratin with keratin-filled cysts
  – variable melanin pigmentation in basilar cells***

Melanoma

• Color or size change of pre-existing mole or new lesions
• Asymmetrical, irregular borders, variegated colors
• Large, irregular nuclei w/clumped chromatin and red nucleoli
• Radial growth first, then vertical growth
  – Degree of vertical growth is predictive of prognosis
• Lymphocytic infiltrate
  – Immune reaction important in controlling progression of tumor
• Assoc. w/p16INK4a

Acanthosis Nigricans

• Clinical features
  – cutaneous marker for associated benign and malignant conditions
  – benign: 80% heritable trait/obesity/endocrine disease/rare congenital syndromes
  – malignant type: underlying adenocarcinoma
  – hyperpigmented zones of skin involving flexoral areas – axilla, skin folds of neck, groin, and anogenital areas

• Pathogenesis
  – may be associate with abnormal production of epidermal growth factors
### Keratoacanthoma

- **Clinical features**
  - rapidly developing benign neoplasm; 1-several cm.
  - resembles squamous cell carcinoma but may heal spontaneously
  - flesh-colored, dome-shaped nodules with central, keratin-filled plug
- **Pathologic features**
  - keratin-filled crater surrounded by lip of proliferating epithelial cells
  - atypical, eosinophilic, "glassy" cytoplasm; stromal response with inflammatory cells
  - host response may determine regression or progression

### Adnexal Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Apocrine gland</th>
<th>Forehead, scalp</th>
<th>Islands of basaloid cells that fit together like jigsaw puzzle; fibrous, dermal matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cylindroma</strong></td>
<td>Apocrine gland</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyadrenoma papilliferum</strong></td>
<td>Apocrine gland</td>
<td></td>
<td>Ducts lined by apocrine type cells</td>
</tr>
<tr>
<td><strong>Syringoma</strong></td>
<td>Eccrine gland</td>
<td>Multiple, small, tan papules on lower eyelids</td>
<td>Eccrine ducts lined by membranous eosinophlic cubicles</td>
</tr>
<tr>
<td><strong>Trichoepithelioma</strong></td>
<td>Hair follicle</td>
<td>Pale, pink glassy cells; resembles uppermost portion of hair follicle</td>
<td></td>
</tr>
<tr>
<td><strong>Sebaceous adenoma</strong></td>
<td>Sebaceous gland</td>
<td></td>
<td>Cytoplasmic lipid vacuoles;</td>
</tr>
</tbody>
</table>

### Skin Cancer

- **Squamous cell carcinoma**
  - Sharply defined, red scaly lesions
  - Sheets w/keratin pearls and intracellular bridging
  - Can involve oral mucosa
  - Assoc w/p53, immunosuppression, HPV, UVB, dysfxn of Langerhans cells
- **Basal cell carcinoma**
  - Pearly papules, telangiectasia
  - Local destruction and invasion of bone and sinuses
  - Palisading cells in tumor nests and tongues
  - Lymphocytic infiltrate
  - Familial: two hit hypothesis
  - Sporadic: PTCH, p53

### Acute Dermatoses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Type of hypersensitivity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urticaria and angioedema</strong></td>
<td>Type I hypersensitivity</td>
<td>Injected or systemically distributed antigen</td>
</tr>
<tr>
<td><strong>Eczema</strong></td>
<td>Type IV hypersensitivity</td>
<td>Contact or systemically distributed antigen</td>
</tr>
<tr>
<td><strong>Erythema multiforme</strong></td>
<td>Type IV hypersensitivity</td>
<td>Systemically distributed antigen</td>
</tr>
</tbody>
</table>

### Urticaria and Angiodema

- **hives**: raised, pale, well-delimited pruritic areas; appear/disappear within hours
  - represent edema of the superficial portions of the dermis
- **angioedema**: egglike swelling with prominent involvement of deeper dermis and subcutaneous fat
- Worse in areas of rubbing and warmth, skin folds due to increased vascular flow (waistband, neckline, under breasts, etc.)
- Vascular reaction mediated by vasoactive substances
  - degranulation of mast cells: IgE-mediated allergic responses or complement-mediated responses
  - direct release of histamine by physical stimuli (cold)
  - non-specific release of mediators by mast cells by drugs or neurological response

### Acute Eczematous Dermatitis

- **Type IV cell-mediated hypersensitivity; prototype: poison ivy**
  - immunologically specific, mononuclear, inflammatory response that reaches its peak 24 to 48 hour after antigenic challenge
  - intensely pruritic, fiery red, with numerous vesicles
  - “eczema” means to boil-over – redness, oozing plaques, vesicle formation
- requires previous sensitization: develops 7-10 days after 1st challenge; 2-3 days on subsequent challenge
- evolution of lesions from acute inflammation to chronic hyperplastic lesions
  - initial edematous inflammation
  - epidermal spongiosis and microvesicular formation
  - chronic: hyperplasia and hyperkeratosis (acanthosis)
  - prone to bacterial superinfection
Erythema multiforme
- self-limited hypersensitivity to certain infections and drugs
- multiform lesions: macules, papules, vesicles, or bullae
- associated infections, drug hypersensitivities, tumors, collagen vascular diseases.
  - penicillin, sulfonamides, barbiturates, salicylates, hydantoins, antimalarials
  - lupus, dermatomyositis, periarteritis nodosa
- bilateral involvement of extremities (especially shins)
- lymphocyte-mediated epidermal necrosis
  - accumulation of lymphocytes at dermal-epidermal border with dermal edema
  - epidermal necrosis, blister formation; sloughing with shallow erosions
- variants
  - febrile disease in children: Stevens-Johnson Syndrome
  - toxic epidermal necrolysis

Pemphigus vulgaris
- separation of stratum spinosum from basal layer
- vesicle contains lymphocytes, macrophages, eosinophils, neutrophils and rounded keratinocytes ("acantholytic cells")
- IgG autoantibodies to intercellular substance of the epidermis (desmoglein)
- may be associated with other autoimmune diseases such as myasthenia gravis, SLE

Bullous pemphigoid
- subepidermal, large tense blisters with erythematous base
- subepidermal, non-acantholytic blisters
- roof of vesicle is lamina densa
- eosinophils predominate cell along with fibrin, lymphocytes, neutrophils
- mast cell migration from venule toward epidermis
- autoimmune disease characterized by circulating IgG antibodies to glycoprotein of lamina lucida
- linear deposition of complement, recruitment of neutrophils, and release of major basic protein

Epidermolysis bullosa
- hereditary
- formation of blisters at sites of minor trauma
- subepidermal vesicle with few inflammatory cells in dermis
- Classification
  - epidermolytic epidermolysis bullosa:
    - within basal keratinocytic layer, with intact epidermis
  - junctional epidermolysis bullosa:
    - within lamina lucida
  - dermolytic epidermolysis bullosa:
    - roof of vesicle is lamina densa
- involve extensive flaws in the dermal component of the basement membrane zone and structural proteins of anchoring filaments, lamina densa

Psoriasis
- common, familial (1-2% of population in US)
- large, erythematous, scaly plaques with silvery scales
  - commonly observed on extensor-dorsal surfaces, Nail changes occur in 30%
- severe disease may be associated with arthritis, myopathy, enteropathy, etc.
- Pathogenesis (T-cell mediated):
  - Deregulation of epidermal proliferation & an abnormality in the dermal microcirculation
  - increased TNF associated with lesions; TNF-antagonists provide significant improvements

Psoriasis
- Pathology (Entire skin is abnormal)
  - thickened epidermis (hyperkeratosis and parakeratosis) with a thinned/absent stratum corneum. Dilated and Tortuous Capillaries
  - Elongated papilla with Munro’s abscesses
  - collections of neutrophils at top of elongated papillae
  - collections of acute inflammatory cells in epidermal spinous layer & mononuclear inflammatory cells in dermis
  - Auspitz’ sign – multiple, minute bleeding points when a scale is removed
Lichen Planus

- Multiple, symmetrically distributed “pruritic, purple, polygonal papules”
  - Usually appear on the flexor surface of the wrists
  - Resolve in 1-2 years
- Pathologic features
  - Prominent band-like lymphocytic infiltrate along dermoepidermal junction which replaces papillary/retie ridge
  - Degeneration of basal keratinocytes; Saw-toothing of dermal interface
  - Fibrillary, eosinophilic bodies represent dead keratinocytes: Colloid, Civatte, or Sabouraud bodies
  - Hypergranulosis and hyperkeratosis
- Wickham striae = white dots or lines
- Pathogenesis = likely T-cell mediated immune reaction to antigens in basal layer

Dermatitis herpetiformis

- Urticaria-like plaques with eroded erythematous blisters
  - Occur on the elbows, knees, buttocks: Intensely pruritic
- Adult males (3rd-4th decade)
- Related to HLA-B8/DRW3 haplotype and gluten sensitivity
- Pathologic features
  - Deposits of granular IgA to gliadin at dermal-epidermal interface, mainly at the tips of the dermal papillae
  - Receptor for gluten found in dermal papillae
  - Collection of neutrophils at tips of papillae (microabscesses)

Osteogenesis Imperfecta

- “Brittle bone disease”
- Autosomal dominant
- Deficiencies in type I collagen
- Affects bones, joints, eyes, ears, skin, and teeth
- Extreme skeletal fragility, confused with child abuse
- Major subtypes
  - Type I is most common; autosomal dominant; increased fractures, blue sclerae, hearing loss
  - Basic abnormality is “too little bone”; marked cortical thinning and attenuation of trabeculae

Ostotetrosis

- “Stone bones” or “Marble bone” disease – too much bone formation (too little resorption)
  - Bones lack medullary canal, decreased bone marrow
- Pathologic fractures, Anemia, hydrocephaly, cranial nerve dysfunction
  - Neural foramina small; cranial nerves compressed
  - Abnormally brittle bones; short stature
- Deficient osteoclast activity
  - Diffuse symmetric skeletal sclerosis
- Two forms - "malignant" (autosomal recessive; die shortly after birth); "benign" (autosomal dominant; live to adulthood)

Dwarfism

- Achondroplastic Dwarfism
  - Autosomal dominant; 80% of cases new mutations
  - Most common disease of the growth plate
  - Defect in proliferation of chondrocytes
  - Mutation in FGF receptor; inhibition of cartilage formation
  - Normal trunk length, shortened limbs, enlarged head
  - Prominent forehead; frontossal bossing
  - No changes in longevity, intelligence, or reproductive status
  - Premature closure of growth plate; normal growth hormone levels
- Thanatophoric dwarfism/dysplasia
  - Most common form of lethal dwarfism
  - Mutation in FGF receptor
  - Respiratory insufficiency due to underdeveloped thoracic cavity

Paget’s Disease

- Osteitis Deformans - “matrix metabolic madness”
- Presentation
  - Elderly male
  - Bone pain, axial skeleton – pelvis/skull/femur
  - Cranial nerve compression of nerves, thickened skull (t’hat size)
- Mechanism (?pararmyxovirus)
  - Early phase – inflammatory, Increased osteoclastic resorption with disordered osteoid synthesis
  - Late phase – burned out sclerosis
  - Most serious consequence – development of osteosarcoma (1-10%) – jaw, pelvis, or femur
- Increased alkaline phosphatase, Tile-like mosaic of osteoid formation pathognomonic
- Urinary excretion of hydroxyproline
Osteomyelitis

- Clinical course
  - fever, systemic illness
  - 60% positive blood cultures, radionuclide scans may be helpful if X-rays negative

- Associations
  - Developed countries, dental/sinus infection → bone
  - Compound fractures
  - Toes and feet of diabetics with chronic ulcers; bone surgery
  - Intravenous drug use
  - Underdeveloped countries, hematogenous spread
  - Ends of long bones most common (esp. children); also vertebrae in adults

- Pathogenesis
  - 80-90% (penicillin-resistant) ***Staph. aureus***,
  - complication of sickle cell – Salmonella
  - drug addicts – Pseudomonas
  - infants/neonates – Group B streptococcus
  - TB – vertebrae (Pott’s disease and Psoas abscess)

- Morphology
  - sub-periosteal chronic nidus of infection = Brodie's abscess
  - smoldering infection → osteoblastic activity → Garre’s sclerosing osteomyelitis
  - devitalized bone (sequestra) surrounded by reactive bone formation (invulcrum)
  - draining sinus tracts to surface
    - Squamous cell carcinoma at orifice of sinus tract

Fibrous dysplasia

- benign disorder; risk of pathologic fracture
- localized bone defects found incidentally
- replacement of bone and marrow with abnormal proliferation of haphazardly arranged woven bone
- monostatic (single site) – 70%
  - 70% childhood, arrests at puberty
  - involves ribs, femur, tibia
- polystatic form (multi-site) – 25%
  - begins earlier, may extend into middle age
  - craniofacial in 50%
  - polystatic with endocrinopathy: 3-5%, skin pigmentation (café au lait spots), precocious sexual development = Albright’s

Aseptic Necrosis

- Causes
  - mechanical vascular disruption; thrombosis and embolism; vessel injury
  - corticosteroids; radiation therapy; sickle cell anemia; alcohol abuse

- Morphology
  - cancellous bone, marrow most affected; cortex not affected
  - subchondral wedge-shaped infarcts extending into epiphysis
  - empty lacunae (death of osteocytes)
  - increased bone density (sclerosis)

- Bone pain
- Pieces of dead bone that becomes separated is called a sequestrum

Other

- Aneurysmal bone cyst
  - Solitary, expansile, erosive lesion of bone
  - Adolescent females (2:1)
  - Metaphysis of lower extremity long bones
  - Secondary to localized hemorrhage due to trauma, vascular disturbance, or increased venous pressure
  - Sometimes secondary to tumors or fibrous dysplasia
  - Tenderness and pain with limited range of motion
  - Appears as cyst on x-ray

Osteoporosis

- Reduced bone mass with increased porosity & thinning of trabeculae & cortex
- Involves entire skeleton, but some areas more affected than others
- Increased risk of fractures: femoral neck, vertebral compression fractures, Colles fracture of wrist
- Not detected by x-ray until 30-40% loss; serum calcium, phosphorus, alkaline phosphatase normal
- Rx: estrogen replacement therapy, bisphosphanates, PTH, adequate Vit D & calcium, exercise
Osteoporosis

- **Primary:**
  - senile: normal age-related, steady decline in bone mass after 4th decade
  - reduced replicative potential of osteoblasts relative to osteoclastic break-down
  - loss accentuated by reduced physical activity with age
  - women/whites more severely affected due to lower peak bone mass
  - post-menopausal: decreased estrogen→ increased osteoclast activation and bone degradation
- **Secondary:** hyperparathyroidism, hypogonadism, pituitary tumors, corticosteroids, multiple myeloma

Primary Bone Tumors -- benign

- **Osteoid Osteoma**
  - Interlacing trabeculae of woven bone surrounded by osteoblasts
  - <2 cm in proximal tibia and femur, pain controlled by NSAIDs
- **Osteoblastoma**
  - Same morphology as osteoid osteoma but found in vertebrae
  - Giant cell tumor (20-40)
    - epiphysis of long bones
    - Locally aggressive (necrosis, hemorrhage, reactive bone formation), soap bubble appearance on XR, spindle shaped cells with giant cells (fused osteoclasts)

Primary Bone Tumors -- benign

- **Osteochondroma (exostosis)**
  - Mature bone with cartilagenous cap
  - Men < 25 on metaphysis of distal femur or proximal tibia
- **Enchondroma**
  - Cartilagenous, found on distal extremities (compare with chondrosarcoma)
  - Multiple lesions in familial syndromes (Ollier’s syndrome) – predisposes to osteosarcoma and chondrosarcoma

Primary Bone Tumors -- malignant

- **Osteosarcoma (men 10-20)**
  - metaphysis of long bones
  - Associated with Paget’s of bone, LiFraumeni, bone infarcts, radiation, retinoblastoma, multiple enchondromas
  - Codman’s triangle = elevated periosteum
- **Ewing’s Sarcoma (boys <15)**
  - anaplastic small blue cells (look like lymphocytes: lymphoma, rhabdomyosarcoma, neuroblastoma, oat cell carcinoma)
  - “Onion-skin” of bone and Homer-Wright Rosettes, diaphysis, t(11:22)
  - Medullary cavity; anemia, systemic symptoms (fever)
- **Chondrosarcoma (Men 30-60)**
  - can arise from osteochondroma
  - axial skeleton

Palmar, Plantar, Penile Fibromatoses

- Dupuytren’s contracture (palmar)
  - irregular or nodular subcutaneous thickening of the palmar fascia with fibrosis, deposition of collagen
  - either unilaterally or bilaterally (50%)
  - slowly progressive flexion contracture, mainly of fourth and fifth fingers
- plantar involvement occurs without flexion contracture
- penile fibromatosis (Peyronie’s disease) occurs as a palpable induration or mass on the dorsolateral aspect of the penis
- may be genetic; males>females; 20-25% may stabilize; others may resolve or recur following resection

Desmoid – Aggressive Fibromatosis

- extra-abdominal: musculature of the shoulder, chest wall, back and thigh
- abdominal desmoids
  - Women
  - musculoaponeurotic structures of the anterior abdominal
  - during or following pregnancy
- intra-abdominal desmoids: mesentery or pelvic walls, often in patients having Gardner’s syndrome
- ?reaction to injury, ?genetic factors; may recur if incompletely excised
- unicentric, unencapsulated, infiltrate surrounding structures
- may recur after excision
Other Non-Neoplastic Conditions

- Nodular (Pseudosarcomatous) Fasciitis
  - Reactive fibroblastic proliferation – may occur after trauma
  - Several weeks history of a solitary, rapidly growing, painful mass in extremities
  - Young and middle-aged adults of either sex
  - Attachment to fascia with apparent invasive characteristics

- Traumatic Myositis Ossificans
  - Characterized by presence of metaplastic bone; not restricted to skeletal muscle; not inflammatory; not always ossified
  - Preceded by trauma; most often extremities in young, athletically active males
  - Cured with excision

Lipoma/Liposarcoma

- Lipomas
  - Lipomas are the most frequent soft tissue tumor
  - Peak incidence 5th and 6th decades
  - Arise in subcutaneous tissues, 5% multiple, usually small with delicate capsule

- Liposarcomas - uncommon
  - Arise from primitive mesenchymal cells; no assoc. with adipose tissue
  - Retroperitoneum and deep tissues of the thigh (less frequently in the mediastinum, omentum, breast, and axilla)
  - Peak in 5th to 7th decades
  - Large, multilobulated with projections into surrounding tissues; cystic softening, hemorrhage, and necrosis are common
  - Large, bulky tumors of deep tissues or cavities often recur after resection; well-differentiated forms metastasize late or not at all

Leiomyoma/Leiomyosarcoma

- Leiomyoma
  - >95% of leiomyomas in female genital tract
  - In addition to female genital tract, leiomyosarcomas occur in the retroperitoneum, wall of the gastrointestinal tract, and subcutaneous tissue
  - Benign - small, multiple, adolescence and early adulthood

- Leiomyosarcoma
  - Malignant – uncommon
  - Superficial - good prognosis; deep - poor prognosis
  - Histologically, leiomyosarcoma is differentiated from leiomyoma by the number of mitoses per high power field

Rhabdomyosarcoma

- Rhabdomyosarcoma
  - Children; one of more common soft tissue tumors in head/neck/urogenital areas; highly malignant
  - Rapidly enlarging masses located near surface of body
  - Deep neoplasms grow to large masses; 20-40% have metastases at diagnosis
  - Sarcoma Botryoides - variant of embryonal form; grapelike clusters, occurs in children under 10; nasopharynx, bladder, vagina
  - Stain with vimentin

- Synovial Sarcoma
  - Multipotential mesenchymal cells, not synovial cells
  - Develop in vicinity of large joints (knee); deep seated mass that has been noted for several years; morphologically resembles synovium
  - t(X;18) translocation

Vulva

- Bartholin cyst - acute infection of Bartholin gland may lead to blocked duct with abscess; excise or permanently open duct
- Vulvar vestibulitis - glands at posterior introitus can be inflamed; chronic, recurrent condition is very painful and can lead to small ulcerations; surgical removal of inflamed mucosa may help
- Lichen simplex chronicus—aka hyperplastic dystrophy
  - Results from chronic rubbing/scratching secondary to pruritus
  - Can occur in eczema, psoriasis, nervousness, etc.
  - Thickening of vulvar squamous epith. and hyperkeratosis
  - Not precancerous

- Lichen sclerosus—aka chronic atrophic vulvitis
  - Thinning of epidermis, degeneration of basal cells, replacement of dermis with fibrous tissue and lymphocytic infiltrate
    - Lymphocytic cell infiltrate → underlying dermal fibrosis
    - Epidermis becomes thinned, scarred, and hyperkeratotic
    - Skin is pale gray and "parchment-like"
    - Labia is atrophied
    - Most common after menopause
    - Not precancerous, but risk of subsequent carcinoma is 1-4%
Vulva – Neoplasms of the Vulva

- **Papillary hidradenoma**
  - Most common benign tumor of the vulva
  - Presents as a nodule at labia majora or interlabial folds with tendency to ulcerate and bleed
  - Consists of tubular ducts with myoepithelial layer characteristic of sweat glands and sweat gland tumors
  - Cure is via simple excision

- **Condyloma acuminatum** — benign sq. cell papilloma
  - Caused by HPV (usually types 6 and 11)
  - A proliferation of stratified squamous epithelium
  - Wartlike lesions, usually multiple and coalescing
    - koilocytic atypia (nuclear atypia and perinuclear vacuolization)
    - In healthy individuals, it will regress
  - **Vulvar carcinoma** — rare; 3% of all female genital ca; 85% squamous cell
    - Peak occurrence in older women
    - Preceded by pre-malignant changes
      - Vulvar intraepithelial neoplasia (VIN) 1-3, and/or vulvar dystrophy
    - Associated with high risk HPV (types 16, 18, 31, 33)
      - Same ones that cause sq. cell CA of the cervix and vagina
      - Other HPV types cause papillomatous lesions elsewhere
    - Associated with squamous cell hyperplasia and Lichen sclerosus

Vulva - Cancer

- **Extramammary Paget Disease**
  - Large tumor cells in epidermis of labia majora demarcated from normal epithelial cells
  - Present with pruritic, red, crusting, sharply demarcated area
  - Cells show apocrine, eccrine and keratinocyte differentiation
  - Clear cells containing glycogen
  - Sometimes associated with underlying adenocarcinoma of the apocrine sweat glands

Vagina

- **Atresia/total absence** (extremely rare)
  - Deformed/non-functioning vagina, or total lack of vagina (vaginal agenesis)
  - Usually manifests at puberty due to amens
  - Disruption of uterovaginal flow requires emergent surgery

- **Septate/double vagina**
  - Rare; failure of total fusion of mullerian ducts (longitudinal septum), or the failure of mullerian ducts to fuse with the urogenital sinus (transverse septum)
  - May be asymptomatic
    - A transverse septum is more likely to block uteran outflow and result in amenorrhea

Vagina

- **Gartner duct cyst**
  - Retention cyst arising from Gartner’s ducts occurring along the remnants of Wolffian ducts
  - Usually asymptomatic and small

- **Vaginal intraepithelial neoplasia (VAIN) — CIN of the vagina**
  - Precancerous lesion; high risk papilloma viruses (types 16, 18), may be multicentric
    - (analogous to high-grade CIN)
    - 10-30% associated with squamous neoplasm in vulva or cervix
  - Graded as mild, moderate, or severe
    - White or pigmented plaques on the vagina
  - Risk of progression to invasive cancer with age/immunosuppression

- **Squamous cell carcinoma**
  - Rare; (0.6/100,000 yearly)
  - 95% squamous cell, upper posterior vagina
  - Usually due to extension of sq. cell CA of the cervix or vulva
    - #1 risk factor — sq. cell CA in cervix or vulva
    - Vagina usually not the primary site
### Vagina

**Adenocarcinoma (clear cell variant)**
- Clear cell variant found in daughters of mothers who took diethylstilbestrol (DES), an anti-abortificant (only 0.14% develop it)
- Presents age 15-20
- Vaginal adenosis = precursor to clear cell adenocarcinoma

**Embryonal rhabdomyosarcoma**
- <5 yo; tumor of malignant embryonal rhabdomyoblasts; bulky mass
- may fill and project out of vagina (sarcoma botryoides)
  - Projection resembles a "bunch of grapes"

### Cervix

**Endocervical polyps**
- Soft, mucoid polyps w/loose, fibromyomatous stroma
- inflammatory proliferation of cervical mucosa – NOT TRUE NEOPLASMS
- found in 2-5% of adult women
  - Most in endocervical canal; may protrude thru os
  - Protrusion can lead to irregular spotting and post-coital bleeding
- associated with dilated mucous-secreting endocervical glands
- inflammation, squamous metaplasia
- Tx - simple curettage or surgical excision

**Cervical Intraepithelial Neoplasm (CIN)**
- HPV most important agent (95% of cervical ca), but NOT only factor in development of
- Viral gene product E6—interrupts cell death cycle by binding p53
- E7—bind RB and disrupts cell cycle
- CIN stages
  - CIN I – mild dysplasia involving lower 1/3 – raised or flat lesion, indistinguishable from condylomata acuminate
  - CIN II – moderate dysplasia – atypical cells in lower 2/3
  - CIN III – severe dysplasia/ carcinoma in situ (if it’s full thickness)
  - **Koilocytes may be present at all stages**
- Takes 10 years to go CIN I → CIN II
- Takes another 10 to go CIN II → CIN III

**Squamous cell carcinoma – 95% of cervical cancer**
- Peak occurrence in middle aged women
- Usually from pre-existing CIN at squamocolumnar junction
- PAP decreases mortality via early detection of CIN and CA
- Intraepithelial and invasive neoplasm
- 3 forms - fungating (exophytic), ulcerating, infiltrative
- extends by direct continuity
- metastasizes to lymph nodes; liver, lungs, bone marrow
- PAP decreases mortality via early detection of CIN and CA
- Histology - 95% large cells, keratinizing or non-keratinizing

### Clinical Course/Management
- Symptoms - irregular vaginal bleeding, leukorrhea, bleeding or pain on coitus; dysuria
- PAP smear is insufficient for prevention/diagnosis
- All abnormalities visualized by colposcopy
- Acetic acid application will reveal CIN
  - White patches of cervix; follow up with punch biopsy
- CIN I - Pap smear follow-up
- CIN II, III – cryotherapy, laser, loop electrosurgical excision procedure (LEEP), or cone biopsy
- Invasive CA - hysterectomy and/or radiation (depends on stage)
- Survival: 80-90% stage I; 75% stage II; 35% stage III; 10-15% stage IV

**Endometrial Hyperplasia**
- Abnormal proliferation of endometrial glands, usually caused by excess estrogen stimulation
- Excess estrogen may be due to...
  - Anovulatory cycles, polycystic ovary dz, estrogen-secreting ovarian tumors (ex. granulosa cell tumors), and estrogen replacement therapy
- Manifest clinically with postmenopausal bleeding
- Can be a precursor lesion of endometrial carcinoma
  - Risk of CA directly correlated with degree of cellular atypia
- Simple hyperplasia (aka cystic or mild) rarely leads to carcinoma
  - high grade (atypical or adenomatous + atypia) - cellular atypia, irregular epithelium; 25% lead to carcinoma
### Female Genital Uterus

**Endometrial Carcinoma:**
- Most common invasive cancer of female genital tract and has best prognosis
- Associated with prolonged estrogen stimulation, nulliparity, diabetes, obesity, hypertension, infertility
- 55-65 year old women; present with bleeding
- Most are well differentiated with a glandular pattern (85% adenocarcinoma), can be polyploid or diffuse
  - Less common variants: papillary serous - older women, more aggressive; tumors with squamous elements
- Most forms spread by direct extension, metastasize late

**Endometrial Polyps:**
- benign sessile masses of any size
- Asymptomatic or irregular bleeding
- Most common cause of menorrhagia 20-40 age group
- Two types - functional endometrium or cystic hyperplastic
- association with endometrial hyperplasia and tamoxifen

**Hyperestrinism**
- Anovulatory cycles: excessive estrogen stimulation relative to progesterone
  - associated with polycystic ovarian syndrome, obesity, malnutrition, systemic disease
  - Common at menarche and perimenopausal
- Inadequate luteal phase: deficient progesterone production by corpus luteum
  - Manifests as infertility, menorrhagia or amenorrhea
- Iatrogenic: oral contraceptives, estrogen replacement

**Proliferative Phase**
- estrogen mediated
  - proliferation of glands and stroma

**Ovulation**
- stimulated by LH surge
  - Confirmed by: basal vacuolization of epithelium, secretory or predecidual changes

**Secretory Phase**
- progesterone mediated
  - Most prominent during 3rd week, tortuous glands and spiral arterioles; 4th week shows exhaustion and gland atrophy

**Menstrual Phase**
- prostaglandin mediated
  - Prostaglandins \( \rightarrow \) vasospasm and necrosis \( \rightarrow \) spasm of the myometrium
  - basal layer remains, upper 2/3 of endometrium shed

### Female Genital Uterus

**Leiomyoma** (fibroids)
- Most common tumors in women
- Reproductive age; blacks>whites
- Estrogen sensitive
- characteristic whorled pattern of smooth muscle bundles
- Often asymptomatic; may cause bleeding, infertility

**Leiomyosarcoma**
- 40-60 year olds; not preceeded by leiomyoma; rare
- characterized by cellular atypia and high mitotic index
  - >10 mitoses per high power field (400X)
- metastasis to lungs, bone, brain, and abdomen

### Fallopian Tubes

**Inflammation**
- PID causes suppurative salpingitis, may result in hydrosalpinx; *N. gonorrhoeae* – 60% of cases, *C. trachomatis* also common
  - Complications: infertility, adhesions

**Neoplasia**
- paratubal cysts – Mullerian duct remnants form hydatids of Morgagni found in fimbria and ligaments; translucent and filled with serous fluid
  - Uncommon: adenomatoid, papillary adenocarcinoma
### Testicular Cancer
- **Sex Cord-Stromal Tumors** (5%):
  - Leydig (Interstitial) cell tumor:
    - 20-60 years old, most benign, androgen producing
    - Presents as testicular swelling, gynecomastia or precocious puberty
    - Brown, homogenous, circumscribed nodules; Reinke crystals
  - Sertoli cell tumor (Androblastoma):
    - Gray-white, homogenous, trabeculae resemble seminiferous tubules
    - Secrete androgens, but not clinically significant; benign

### Endometriosis
- Presence of endometrial glands/stroma outside of the uterus
- Found in ovaries, uterine ligaments, rectovaginal septum, pelvic peritoneum
- Common cause of infertility
- Dysmenorrhea, dyspareunia, dyschezia
- Tissue under hormonal control = cyclic changes w/ bleeding during normal menstrual cycle
- "chocolate cysts" in ovaries (blood, lipid debris); scarring of fallopian
- Likely causes: Retrograde menstruation, Differentiation of dispersed coelemic epithelium, Lymphohematogeneous spread

### Ectopic Pregnancy
- Implantation of fetus in any site other than uterus
  - Tubes (90%), ovary, abdominal cavity, cornual end
- Predisposing factors – PID w/ chronic salpingitis (35-50%), peritubal adhesions from appendicitis or endometriosis, leiomyomas, previous surgery, IUD
- Embryo undergoes usual development, but placenta is poorly attached, may separate and cause hematosalpinx or rupture
- Presents most commonly with pain, pelvic hemorrhage, shock, sx of acute abdomen – MEDICAL EMERGENCY!

### Polycystic Ovary Disease
- Previously known as Stein-Leventhal syndrome
- Numerous cystic follicles
- Persistent anovulation, obesity, hirsutism, and rarely virilism
- Ovaries (bilateral) 2x normal size and studded w/subcortical cysts; theca interna hyperplasia; **Corpora Lutea ABSENT**
- LH stimulation of theca lutein cells → excessive production of androgens which is converted to estrogens
- Caused by unbalanced or asynchronous release of LH by pituitary: ↑ LH, ↓ FSH, ↑ testosterone
- Associated w/ Insulin resistance; ↑ risk of endometrial cancer; prolactinoma may be involved in 25%

### Ovarian Epithelial Tumors
- 65-70% overall frequency, 90% of malignant ovarian tumors
- Histology: cystadenomas, cystadenofibromas, adenofibromas
- Risk of malignancy increases w/ amount of solid epithelial growth
- Clinical signs: low abdominal pain/enlargement, GI complaints, urinary complaints, ascites w/ peritoneal extension (exfoliated cells in fluid)
- Metastasis to liver, lungs, GI, regional nodes, opposite ovary common
- 80% of serous and endometrioid tumors positive for CA-125
- BRCA is a marker for increased risk
- Fallopian tubal ligation and OCT reduce relative risk

### Ovarian Epithelial Tumors
- **Serous tumors**
  - Tall, ciliated columnar epithelial lined serous fluid filled cysts, on surface of ovary
  - Can be benign or borderline (age 20-50) or malignant (>50)
  - Serous cystadenocarcinomas are most common malignant ovarian tumor (40%)
  - Often bilateral and contain psammoma bodies
  - Benign: smooth cyst wall, no epithelial thickening
  - Borderline: increasing papillary projections into cyst, some nuclear atypia, no destruction of stroma
  - Peritoneal spread w/ desmoplasia causing intestinal obstruction
Ovarian Epithelial Tumors

- **Mucinous tumors**
  - Rare before puberty or after menopause
  - Large number of big cysts filled with glycoproteins, not on surface, not bilateral, tall columnar epithelium without cilia
  - Associated with pseudomxoma peritonei: extensive mucinous ascites
- **Endometrioid tumors**
  - Unlike mucinous and serous, most are endometrioid tumors are malignant
  - Contain tubular glands that resemble endometrium
  - Combination of cystic and solid areas, 50% bilateral
- **Clear Cell Adenocarcinoma**
  - Large cells with clear cytoplasm

**Ovarian Epithelial Tumors**

- **Cystadenofibroma**
  - Pronounced desmoplasia underlying columnar epithelial neoplasia
  - Metastatic spread is uncommon
- **Brenner tumors**
  - Uncommon transitional cell tumors, sometimes found with mucinous cystadenomas
  - Usually unilateral, can become quite massive
  - Sometimes surrounded by plump fibroblasts with hormonal activity
  - Can secrete estrogens

**Stromal Ovarian Tumors**

- **Ganulosa-Thecal (mixed: gran=malignant, thecal=benign)**
  - Sheet/cords of cuboidal to polygonal cells
  - Call-Exner bodies: small follicles w/eosinophilic secretions
  - Estrogen secreting: precocious puberty
  - Assoc. w/endometrial hyperplasia/carcinoma (adult women)
- **Thecoma-Fibroma (benign)**
  - Solid, bundles of spindle shaped fibroblasts w/lipid droplets
  - Meig’s Syndrome: R-sided hydrothorax, ovarian tumor, ascites
  - Hormonally inactive
  - Assoc. w/ basal cell nevus syndrome

**Teratomas**

- Germ cell tumor with all three germ layers
- From totipotent cells → usually found in gonads
- 3 categories:
  - Mature (benign) – most are cystic (dermoid cysts), tissue resembles adult tissue, unilateral, karyotype 46,XX, reproductive females
  - Immature (malignant) – rare, tissue resembles fetal or embryonic tissue, adolescent women
    - Frequently metastasize through capsule
  - Monodermal (specialized) – rare, unilateral, may be functional
    - struma ovari – thyroid tissue, can cause hyperthyroid
    - ovarian carcinoid – from intestinal epithelium, produces 5-HT

**Non-Neoplastic Breast Disease**

**FIBROCYSTIC CHANGE:**
- Most common breast condition
  - bilateral/multiple formation of blue-domed cysts that result in pain/tenderness that varies cyclically
  - causes microcalcification (confused with cancer)
**GYNECOMASTIA:** most commonly caused by cirrhosis; usually unilateral

**Proliferative Disease:** proliferation of epithelial/glandular tissue; increased risk for carcinoma if >4 epithelial layers or atypia

**Sclerosing Adenosis:** increased numbers of acini compressed by fibrous tissue (silt-like); slight increase in cancer
### Inflammatory Breast Disease
- Fat necrosis: trauma-related; chalky, white, hard lesions from saponification
- Lactation Mastitis: staph infection from nursing; may → abscess
- Galactocele: cystic dilation with viscous “milk” after lactation cessation
- Mammary Duct Ectasia: interstitial granulomatous inflammation leading to duct dilation; thick/sticky nipple discharge, lump/retracted nipple; post-menopause
- Granulomatous Mastitis: epithelial granulomas in multiparous women; may be a hypersensitivity reaction secondary to lactation
- Silicone Breast Implants: → chronic inflammation/fibrosis

### Ductal Breast Carcinoma
- Typically divided into Ductal Carcinoma in Situ (DCIS) and Invasive Ductal Carcinoma
- DCIS: periductal concentric fibrosis with chronic inflammation
  - Linear or branching microcalcifications seen on mammography; associated with intraductal necrosis
- Invasive: streaks of white elastic stroma with foci of calcification; irregular borders signifying escape from the ductal basement membrane; highly scirrhous, desmoplastic tumor
- If mass is palpable, half of patients will have lymph node metastasis
- Fixation to chest wall, lymphedema → peau d’orange, cooper ligament tethering to skin, retraction of nipple

### Non-ductal breast carcinoma
- **Lobular carcinoma in-situ**
  - Proliferation in one or more terminal ducts – distended lobules
  - Incident finding on biopsy for another reason – nonpalpable
  - Often multifocal and bilateral, can progress to carcinoma
  - No cell adhesion – lack e-cadherin
- **Invasive lobular carcinoma**
  - Tends to be bilateral and multicentric
  - Single file cells, can be concentric and have bull’s eye appearance
  - Present as palpable mass or density on mammogram
  - Well differentiated tumors express hormone receptors

### Non-ductal breast carcinoma
- **Medullary carcinoma**
  - Associated with BRCA-1 mutation
  - Bulky, soft tumor with large cells and lymphocytic infiltrate
- **Colloid carcinoma**
  - Occurs in older women, grows very slowly
  - Cells surrounded by extracellular pale gray-blue mucin
- **Tubular Carcinoma**
  - Women in late 40’s
  - Well-formed tubules in terminal ductules
  - Absence of myoepithelial layer
  - Multifocal or bilateral tumors

### Spontaneous abortions
- 10-15% of recognized pregnancies; probably close to 22% of all conceptions; chromosomal studies are recommended with habitual or recurrent abortion or with malformed fetus
- **fetal influences**
  - Defective implantation
  - Genetic or acquired developmental abnormality
  - Chromosomal abnormalities in >50%
- **maternal influences**
  - Inflammatory diseases (local and systemic)
  - Uterine abnormalities
  - Infection

### Placenta
- **Placental abnormalities**
  - *placenta accreta* - partial or complete absence of the decidua with adherence of placenta directly to myometrium; failure of placental separation may cause postpartum bleeding (life threatening); up to 60% association with placenta previa; uterine rupture (placenta percreta)
  - *placenta previa* - implantation in the lower uterine segment or cervix associated with serious antepartum bleeding and premature labor
  - *placenta abruptio* - separation of the placenta prior to delivery
- **Twin placenta**
  - Monochorionic implies monozygotic twins; may have one or two amnions
  - Dizygotic twins usually have dichorionic, diamniotic placenta

### Twins placenta
- Placental abnormalities
- *placenta accreta* - partial or complete absence of the decidua with adherence of placenta directly to myometrium; failure of placental separation may cause postpartum bleeding (life threatening); up to 60% association with placenta previa; uterine rupture (placenta percreta)
- *placenta previa* - implantation in the lower uterine segment or cervix associated with serious antepartum bleeding and premature labor
- *placenta abruptio* - separation of the placenta prior to delivery
- **Twin placenta**
- Monochorionic implies monozygotic twins; may have one or two amnions
- Dizygotic twins usually have dichorionic, diamniotic placenta
Pre-eclampsia/eclampsia

- **Pre-Eclampsia**: hypertension, proteinureia, and edema
- **Eclampsia**: add convulsions, CNS disturbances, and DIC
- 6% of pregnant women; last trimester; primiparas
- DIC in eclampsia results in lesions in liver, kidneys, heart, placenta, and brain
- The primary pathology appears to involve inadequate placental blood flow and ischemia; trophoblast-dependent
- HELLP syndrome - hemolysis/elevated liver enzymes/low platelets associated with microangiopathic hemolysis with DIC and fibrin deposition
- Eclampsia is heralded by convulsions. It usually represents vascular damage to the CNS with the development of DIC.
  - Microscopic lesions include arteriolar thrombosis, arteriolar fibrinoid necrosis, petechial hemorrhages, and diffuse microinfarcts.

Complete (Classic) Mole

- characterized by growth and cystic swelling of COMPLETE chorionic villi with trophoblastic proliferation
- NO EMBRYO IS PRESENT; uterus is filled with grape-like clusters; volume is MUCH GREATER than in normal pregnancy
- more than 90% have 46,XX diploid pattern, all derived from the sperm (duplication of uniploid sperm; 46YY not viable)
- proliferation of both cytotrophoblasts and syncytiotrophoblasts
  - grape-like clusters of swollen, watery chorionic villi
  - villi are not atypical in structure
- presents about 14th week (8-24 wk) with vaginal bleeding, uterus larger than normal pregnancy, high HCG levels
- about 10% develop persistent trophoblastic disease and 3-5% WILL DEVELOP CHORIOCARCINOMA

Other Moles

- **Incomplete (Partial) Mole**
  - Villi INCOMPLETELY involved; usually focal
  - karyotype is triploid (69,XY) or tetraploid (92,XXXX)
  - EMBRYO IS VIABLE for weeks, so fetal parts may be found
  - Presentation with nonviable fetus and irregular vaginal spotting, but uterine size NOT increased and NO increased risk of choriocarcinoma
- **Invasive mole**
  - mole that penetrates and may even perforate uterine wall; tumor is locally destructive
  - vaginal bleeding and irregular uterine enlargement; persistent elevated HCG; may present several weeks after a mole has been evacuated
  - hydropic villi may embolize to lungs and brain, but do not grow as true metastases; responsive to chemotherapy

Choriocarcinoma

- epithelial malignancy of trophoblastic cells from previously normal or abnormal pregnancy
- rapidly invasive, widely metastasizing; but responds well to chemotherapy
- 50% arise in hydatidiform (classic) moles (1 in 40 moles), 30% in previous abortions, 22% in normal pregnancies
- no chorionic villi; proliferation of both cytotrophoblasts surrounded by rim of syncytiotrophoblasts
- does not produce large, bulky mass
- produces high levels of HCG in absence of pregnancy
- metastases to lungs, vagina, brain, liver, kidney