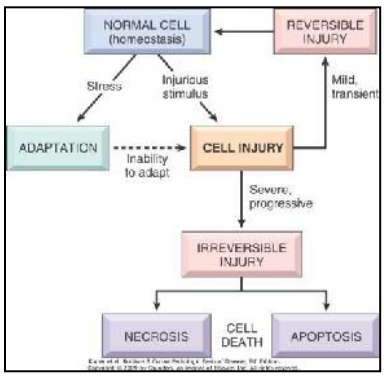
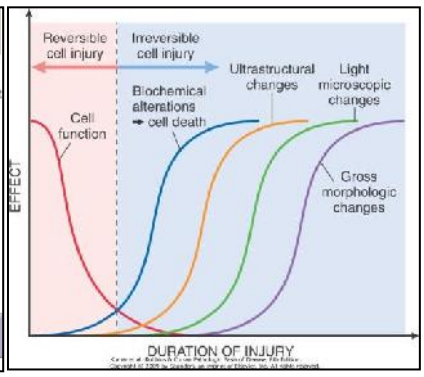
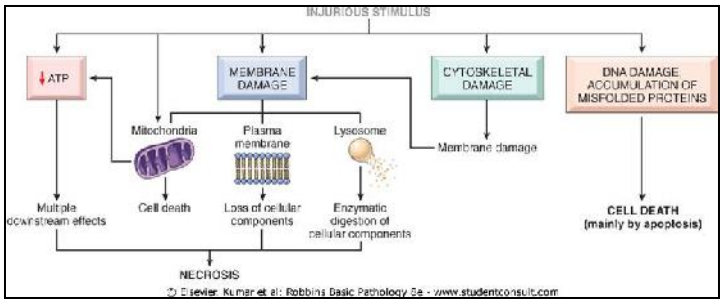
Cell Injury

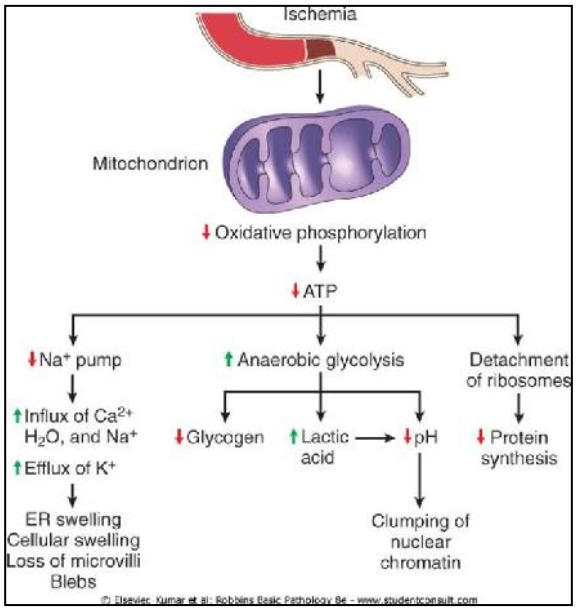


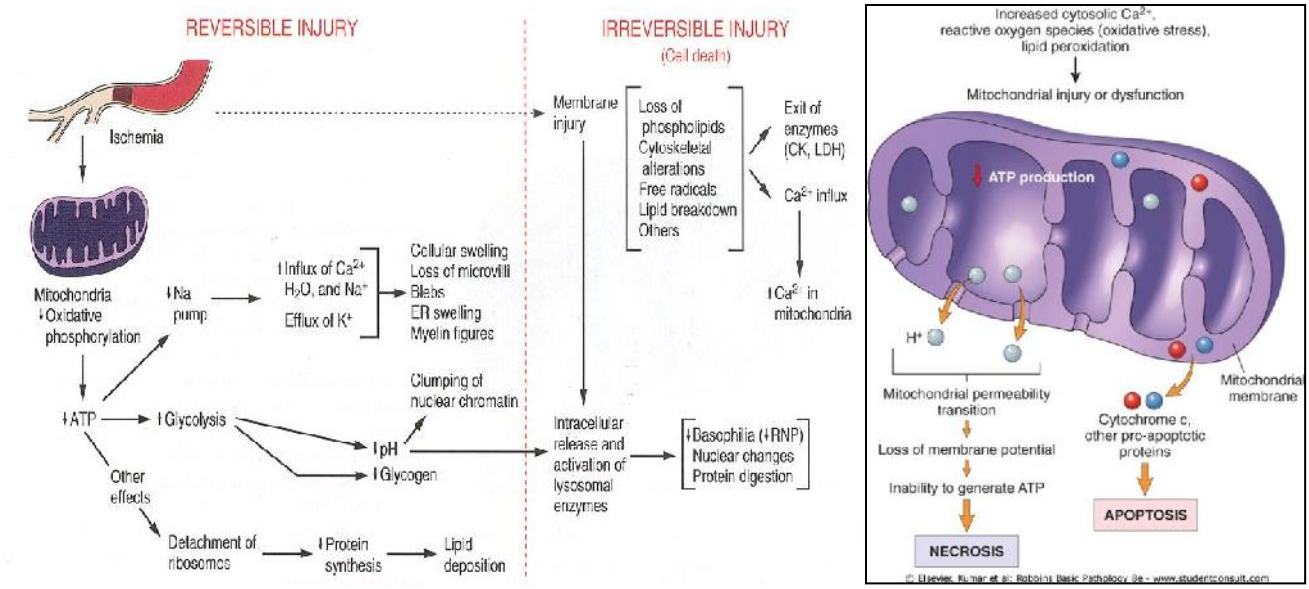


- 4 interrelated cell systems especially susceptible to injury
  - Membranes (cellular and organellar)
  - Aerobic system
  - Protein synthesis (enzymes, structural proteins, etc)
  - Genetic apparatus (DNA, RNA, etc)
- Mechanisms for cell injury
  - Loss of Ca^{++} homeostasis
  - Membrane permeability defects
  - ATP depletion
  - O_2 and O_2 derived free radicals

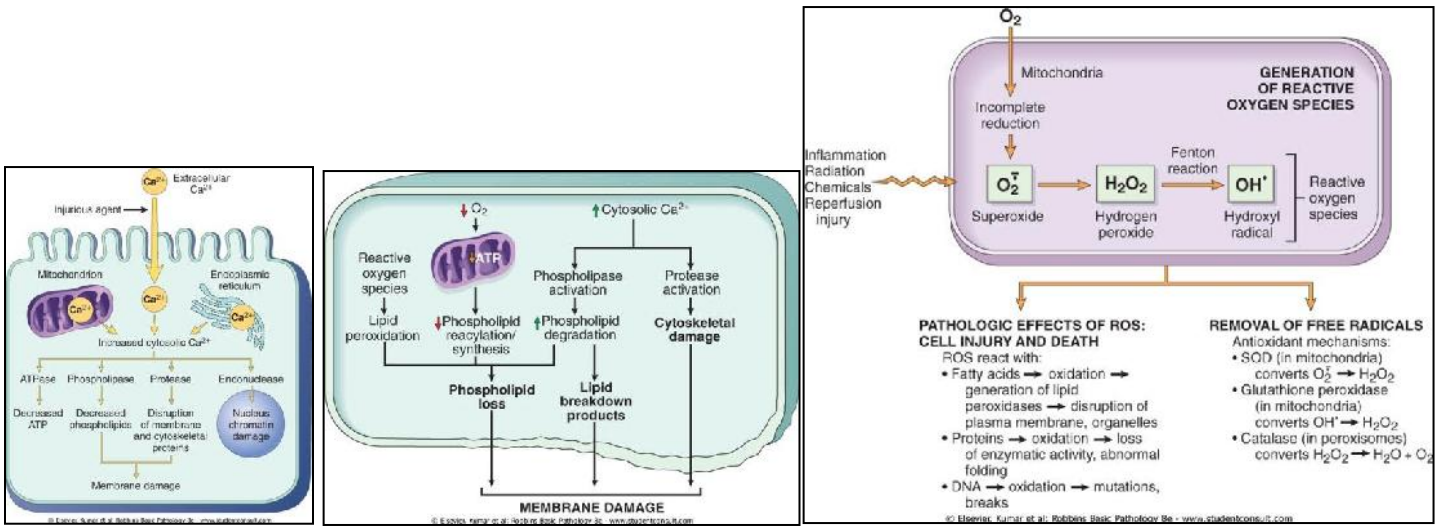


- Causes of Cell Injury
  - Hypoxia (ischemia – block in blood flow, hypoxemia – decreased partial pressure of oxygen in blood, anemia – decreased oxygen carrying capacity)
    Block in ventilation(foreign body), oxygen diffusion (pneumonia, pulmonary edema), perfusion (pulmonary embolus), decreased cardiac output
  - Free radical damage
  - Chemicals, drugs, toxins
  - Infections
  - Physical agents
  - Immunologic reactions
  - Genetics
  - Nutritional imbalance
- Oxygen tension falls disrupts oxidative phosphorylation decreased ATP
  - ↓ Na^+/K^+ ATPase increased intracellular Na^+ swelling
  - ↓ ATP-dependent Ca^{++} pumps increased cytosolic Ca^{++}
  - Depletion of glycogen from altered metabolism
  - Decreased pH from lactic acid accumulation
  - Decreased protein synthesis from ribosome detachment from RER
- End result – cytoskeletal disruption with loss of microvilli, bleb formation, etc



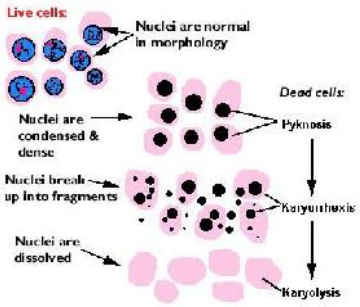


- Excess cytoplasmic Ca^{++} denatures proteins, poisons mitochondria, inhibits cellular enzymes
    - Therefore, membrane damage and Ca^{++} homeostasis is critical

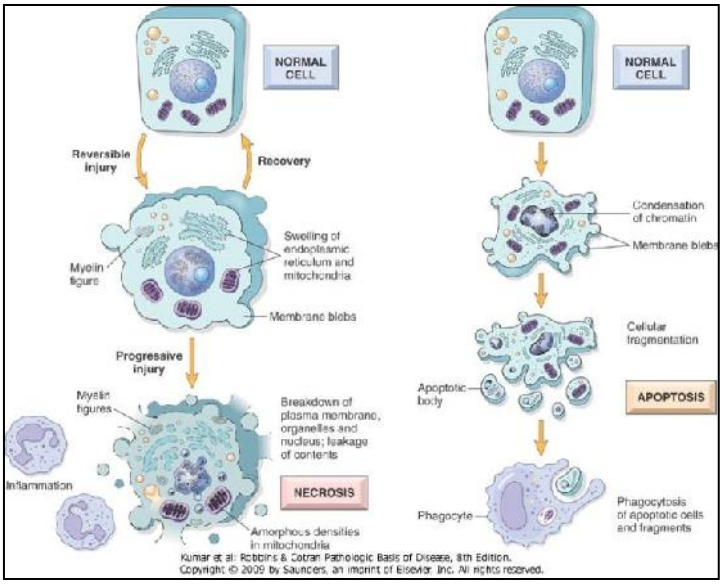


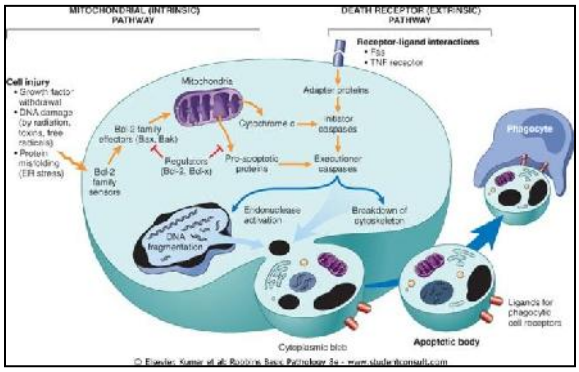
    - Injured membranes allow intracellular components to enter the serum and can be measured
- Free radical injury (acetaminophen – Tylenol overdose)
    - Lipid peroxidation – damage to cellular and organellar membranes
    - Protein crosslinking/fragmentation from oxidative modification of amino acids and proteins
    - DNA damage from free radical reaction with thymine
- Types
    - Chemical
    - Inflammation/microbial killing
    - Irradiation
    - Oxygen
    - Age-related
- Free Radical Derivations
    - Superoxide – $O_2^{\bullet -}$ – produced by cellular oxidases
    - H_2O_2 – produced by superoxide mutase or catalase
    - $OH^{\bullet -}$ – produced by ionizing radiation, H_2O_2 and $O_2^{\bullet -}$, and fenton reaction

- Morphological changes follow functional changes
    - Reversible injury
        - Light microscope – cell swelling, fatty change
        - Ultrastructural changes – cell membrane alterations, swelling and small deposits of mitochondria, RER and attached ribosome swelling
    - Irreversible injury
        - Light microscope
            - Loss of RNA (which is basophilic) – increased cytoplasmic eosinophilia (pink colour)
            - Cytoplasmic vacuolization
            - Nuclear chromatin clumping
        - Ultrastructural
            - Membrane breakage
            - Large amorphous densities in mitochondria
            - Nuclear changes
        - Pyknosis – nuclear shrinkage, increased basophilia (blue colour)
        - Karyorrhexis – fragmentation of pyknotic nucleus
        - Karyolysis – fading of basophilia of chromatin



- Types of Cell Death
    - Apoptosis – usually regulated, may be pathogenic, has a role in embryogenesis
    - Necrosis – always pathologic, many causes
- Apoptosis
    - Programmed cell death in embryogenesis
    - Hormone dependent involution of adult organs (thymus)
    - Cell deletion in proliferative populations
    - Cell death in tumors
    - Cell injury in some viral diseases (hepatitis)





- Necrosis
    - Causes
        - Coagulative (most common)
            - Cells basic outlines are preserved
            - Homogenous, glassy eosinophilic appearance due to loss of cytoplasmic RNA (basophilic) and glycogen (granular)
            - Nucleus may show any of pyknosis, karyorrhexis, or karyolysis
        - Liquefactive – most often in CNS and abscess – usually from enzymatic dissolution of necrotic cells (usually due to release of proteolytic enzymes from neutrophils)

Caseous

- Gross form – resembles cheese
- Micro form – amorphous, granular eosinophilic material surrounded by rim of inflammatory cells (no visible cell outlines, tissue architecture is obliterated)
- Usually seen in infections (mycobacterial and fungal)

Enzymatic fat necrosis

- Hydrolytic action of lipases on fat, most often in and around pancreas, can also be seen in other fatty body areas (usually via trauma)
- Fatty acids released via hydrolysis react with Ca^{++} to form chalky white areas – "saponification"

Gangrenous necrosis

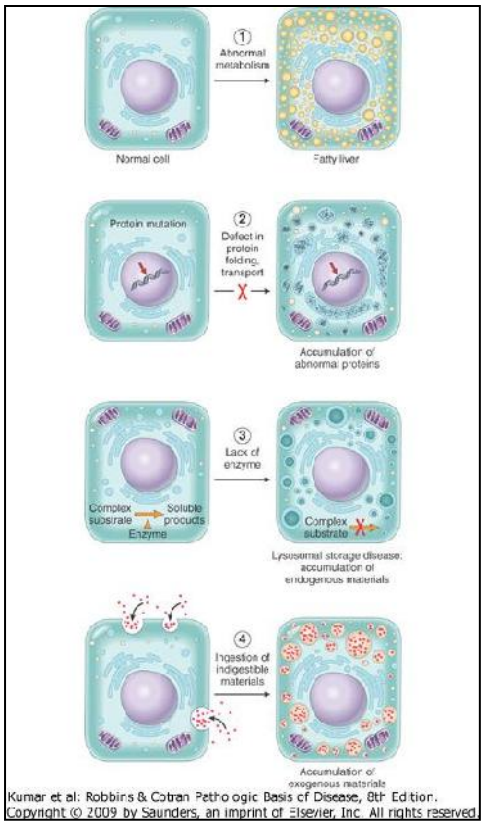
- Most often in extremities via trauma/physical injury
- Dry gangrene – no bacterial superinfection, looks dry
- Wet gangrene – has bacterial superinfection, looks wet and liquefactive

Fibrinoid necrosis

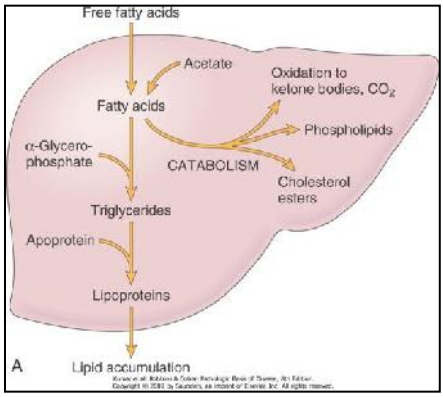
- Usually seen in walls of vessels (vasculitides)
- Glassy, eosinophilic fibrin-like material deposited within vascular walls
- Immune disorders

Cellular Adaptation

- Hyperplasia – increase in NUMBER (not size) of cells in an organ or tissue
    - May be seen in combination with hypertrophy
    - Physiologic hyperplasia – mechanisms include increased DNA synthesis, growth inhibitors will halt hyperplasia after sufficient growth has occurred
        - Hormonal – hyperplasia of uterine muscle during pregnancy
        - Compensatory – hyperplasia in organ after partial resection
    - Pathological – not in itself neoplastic or preneoplastic, but the trigger may place patient at risk of sequelae (dysplasia, carcinoma)
        - Excess hormones – endometrial proliferation from over increased estrogen
        - Excess growth factor stimulation – warts arising from papillomavirus
- Hypertrophy – increase in cell SIZE, leading to increase in organ size
    - Usually in terminal cells which can no longer divide, so their only recourse is enlargement
    - End result is amount of increased work that each cell must perform is limited
    - Physiologic hyperplasia – hormonal stimulation (hypertrophy of uterine wall during pregnancy)
    - Pathologic – chronic cell stressors (stenotic valves, left ventricular hypertrophy from increased afterload)
- Chronic hypertrophy – if stress that triggered hypertrophy is not resolves, likely result is organ failure
    - Hypertrophied tissue at increased risk for ischemia from metabolic demands outpacing blood supply
- Autotrophy – shrinkage in cell size (may or may not include shrinkage of organ size)
    - Cells are smaller than normal, but are still viable. They do not normally undergo apoptosis or necrosis
    - Physiologic autotrophy – tissues/structures present in embryo or childhood may undergo autotrophy as growth and development process progresses
    - Pathologic – decreased workload, loss of innervation, decreased supply, inadequate nutrition, decreased hormonal stimulation, pain, physical pressure
- Metaplasia – REVERSIBLE change in which one type of adult cell (epithelial or mesenchymal) is replaced by another type – if stress/injury abates, metaplastic tissue may revert to original cell type
        - This is a protective mechanism, not a premalignant change
        - Reprogramming of epithelial stem cells (reserve cells) from one type of epithelium to another
        - Reprogramming of mesenchymal (pluripotent) stem cells to differentiate along different mesenchymal path
    - Bronchial (pseudostratifie, ciliated columnar) to squamous epithelium – smokers
    - Endocervical (columnar) to squamous – chronic cervicitis
    - Esophageal (squamous) to gastric or intestinal – barret esophagous (acid reflux)



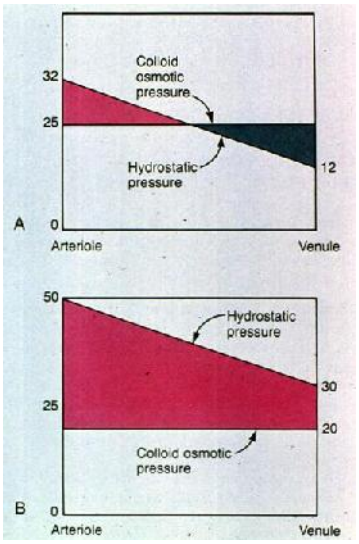
- Intracellular accumulations – transient or permanent, may acquire substances that arise either from cell itself or from nearby cells
    - Normal cellular constituents accumulated in excess from increased production, decreased metabolism, etc (lipid accumulation in hepatocytes)
    - Abnormal substances via decreased metabolism or excretion (storage disease)
    - Pigments via decreased metabolism or transport (carbon, silica)



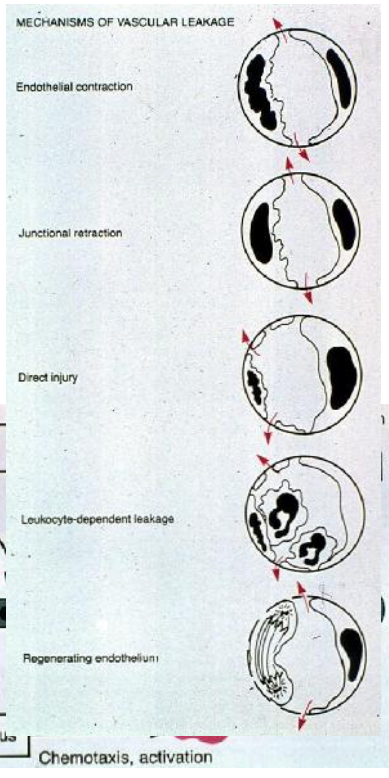
- Lipid accumulation
  - Steatosis (fatty changes) – accumulation of lipids in hepatocytes
    - From ^OH, drugs, toxins
    - Can occur at any step in the pathway
- Cholesterol
  - Seen as needle-like clefts in tissue, washes out with processing so looks cleared out
  - Atherosclerotic plaque in arteries
  - Accumulation in macrophages (called "foamy" macrophages) – seen in xanthomas, areas of fat necrosis, cholesterolosis in gall bladder
- Proteins
  - May be due to cell inability to maintain proper metabolic rate
    - Increased reabsorption of proteins in renal tubules → eosinophilic, glassy droplets in cytoplasm
  - Defective protein folding
    - α-1-AT deficiency → intracellular accumulation of partially folded intermediates
    - may cause toxicity – some neurodegenerative diseases
- Glycogen
  - Intracellular accumulation can be physiologic (hepatocytes) or pathologic (glycogen storage disease)
  - Easiest seen with a PAS strain – deep pink to magenta color
- Pigments
  - Exogenous pigments – anthracotic (carbon) pigments in lungs, tattoos
  - Endogenous pigments
    - Lipofuscin ("wear and tear" pigments)
      - Results from free-radical peroxidation of membrane lipids
      - Finely granular yellow/brown pigment
      - Often seen in myocardial cells and hepatocytes
    - Melanin
      - Only endogenous brown-black pigment
      - Often (not always) seen in melanomas
    - Hemosiderin
      - Hemoglobin derived and represents aggregates of ferritin micelles
      - Granular or crystalline yellow/brown pigment
      - Often seen in macrophages in bone marrow, spleen, liver (lots of RBC and RBC breakdown); also in macrophages in areas of recent hemorrhage
      - Best seen with iron stains (Prussian blue) – makes granular pigment more visible
- Calcification
  - Dystrophic – occurs in areas of nonviable or dying tissue in the setting of NORMAL serum calcium
    - Also occurs in aging/damaged heart valves, atherosclerotic plaque
    - Tissue, not serum, is calcified
    - Gross – hard, gritty, tan-white, lumpy
    - Micro – deeply basophilic H&E stain, glassy, amorphous, may be either crystalline or non-crystalline
  - Metastatic – may occur in normal, viable tissues in the setting of hypercalcemia due to any number of causes
    - Most often seen in kidneys, cardiac muscle, soft tissue
    - Serum, not tissue, is calcified (unlike dystrophic)

Inflammation

- Reaction of vascularized living tissue to local injury
- Reaction of tissues to injury, characterized by clinically by SHaRP and loss of function
    - Pathologically by vasoconstriction followed by vasodilation, stasis, hyperemia, accumulation of leukocytes, exudation of fluid, deposition of fibrin, and according to some sources the processes of repair, the production of new capillaries, and fibroblasts, organization, and cicatrization
- -itis – appendicitis, cellulitis, meningitis, pneumonitis, nephritis, myocarditis
    - Microbial infection – pneumonia, skin infections, etc
    - Physical agents – burns, trauma, cuts, radiation
    - Chemicals – toxins, caustic substances
    - Others – immunological, rheumatoid arthritis
- Acute inflammation - <48h – PMNs
- Chronic inflammation - >48h – mononuclear cells (macrophages, lymphocytes, plasma cells)
    - Exception – abscess, even greater than 48h, always has PMNs
- Acute inflammation
    - Usually involve PMNs are mediators, changes which occur within minutes to days after injury
        - Minor damage – 15-30 minutes
        - Major damage – a few minutes
    - Changes in vascular flow and caliber (hemodynamics)
        - Vasoconstriction – transient, inconstant
        - Vasodilation – first arterioles, then capillaries, then venules
        - Slowed circulation – albumin-rich fluid leaking into extravascular tissue RBC concentration in small vessels and increased blood viscosity
        - Leukocyte margination – PMNs become oriented at vessel periphery and start to stick

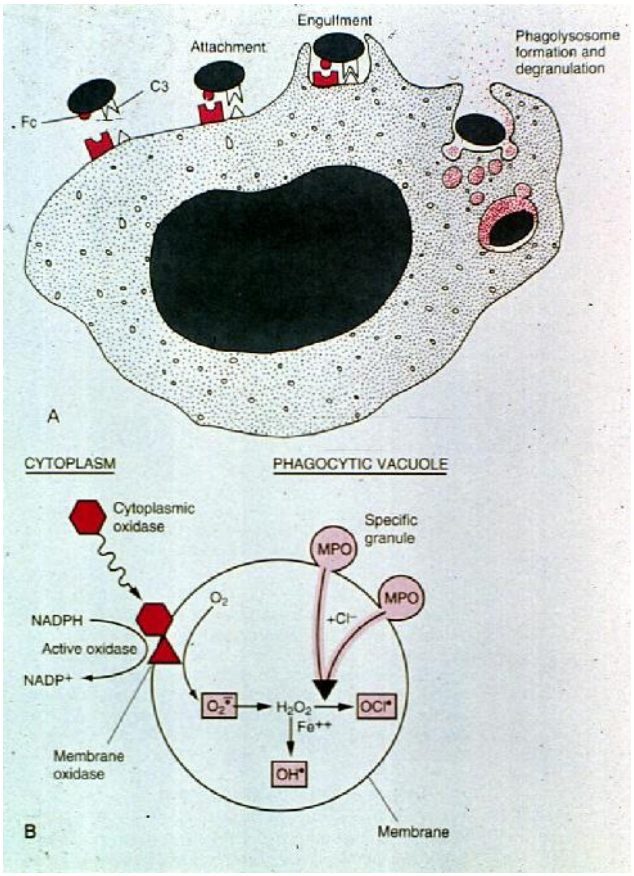


    - Vascular permeability (leakage)
        - Starling's hypothesis – for normal tissue, intravascular hydrostatic pressure ~ colloid osmotic pressure
        - Inflammation – increased intravascular hydrostatic pressure, decreased colloid osmotic pressure – results in edema
    - Leukocyte exudation
        - Margination, rolling, adhesion
        - Diapedesis (transmigration across endothelial border)
        - Migration towards chemostatic agent
        - Phagocytosis



- Lymphatic involvement – responsible for draining edema
    - Edema – excess fluid in interstitial tissue or serous cavities – either transudate or an exudate
        - Transudate – ultrafiltrate of blood plasma
            - Endothelium permeability usually normal
            - Low protein content (usually albumin)
            - Specific gravity < 1.012
        - Exudate – blood plasma filtrate mixed with

inflammatory and cellular debris
Endothelial permeability usually altered
High protein content
Specific gravity > 1.020
Pus – purulent exudate – inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris



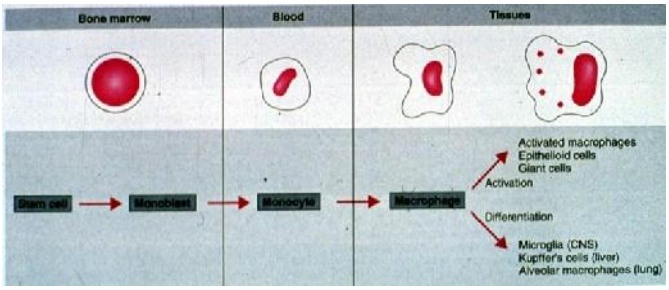
- Phagocytosis
  - Recognition and attachment
  - Engulfment
  - Killing/degradation
    - Oxygen dependent – myeloperoxidase dependent (MOST IMPORTANT), and myeloperoxidase independent
    - Oxygen independent
  - Defects in leukocytes function
    - Margination and adhesion – ^OH, steroids, AR leukocyte adhesion deficiency
    - Emigration towards chemotactic stimulus – drugs, chemotaxis inhibitors
    - Phagocytosis – chronic granulomatous disease (CGD)

- These systems seem to be interrelated – there seems to be a very good system of checks and balances
- Acute inflammation has 4 outcomes
  - Abscess formation
  - Progression to chronic inflammation
  - Resolution – tissue returns to normal
  - Healing – tissue scars or fibrosis

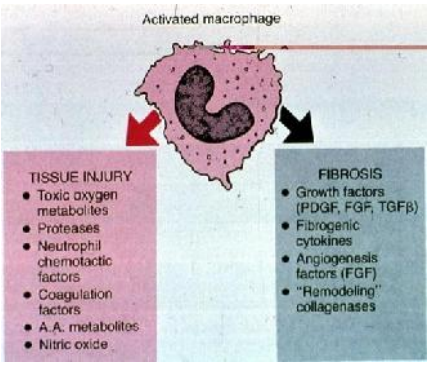
- Abscess – circumscribed collection of pus appearing in an acute or chronic localized infection, and associated with tissue destruction and, frequently, swelling
  - Usually the result of a pyogenic organism
  - A hole filled with goo (usually of dead neutrophils)
  - Abscess is always filled with PMNs, acute or chronic

- Chronic inflammation
    - Greater than 48h – mononuclear cells – primarily macrophages, lymphocytes, plasma cells
  - Arises if various organs in 1 of 3 ways
    - Follows acute inflammation
    - After repeated bouts of acute inflammation (pneumonia)
    - Without prior acute inflammation – exception is that a viral infection ALWAYS elicits lymphocytic response instead of PMNs, even in acute cases (bacteria elicits PMN acute response)

- Histologic chronic inflammation
    - Lymphocytes, plasma cells, macrophages (aka histiocytes, kuppfer cells, etc – are central to chronic inflammation like PMNs are to acute inflammation)
    - Fibroblast proliferation and small vessels
    - Increased connective tissue
    - Tissue destruction

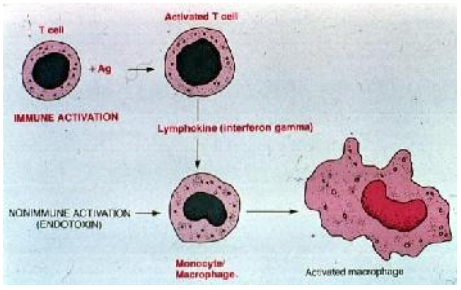


- All macrophages come from the same cell line, but differ in their microenvironment
    - They belong to the mononuclear phagocyte system (RES) – consists of bone marrow, peripheral blood, and tissue
    - All MOs are slower than PMNs – primary reason different cells respond for acute vs chronic
        - Can both phago and pino cytosis
        - Can be activated – especially by lymphokines, T-cells, anything that disturbs cell membrane
            - Allows for more aggressive behavior in inflammation
        - Secrete large quantities of chemical mediators



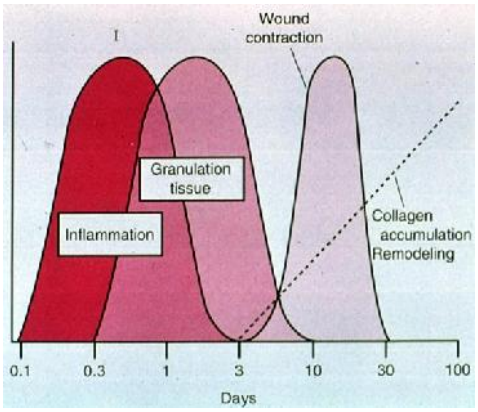
- Macrophage functions
    - Produce toxic, biologically active substances (ex:// O_2 metabolites)
    - Cause influx of other cells (Ex:// other macrophages and lymphocytes)
    - Cause fibroblast proliferation and collagen deposition
    - Phagocytosis
    - Begin emigration during acute phase and are predominant cell type by 48h
- Macrophage accumulation
    - Continued recruitment from circulation – secondary chemotactic factors
    - Cell division
    - Prolonged survival once activated
- Other cells in chronic inflammation – Lymphocytes, Plasma cells, Eosinophils, PMNs

- Chronic granulomatous inflammation and giant cells
    - A type of chronic inflammation defined by *presence of granulomas*, small 0.5-2mm collections of modified "epithelioid" histiocytes/macrophages and (langhan's) giant cells (coalesced histiocytes), usually surrounded by a rim of lymphocytes
- Granumolas occur in response to various diseases – foreign body, TB, fungal, sarcoidosis, schitosomiasis, leprosy
    - 2 factors needed for granuloma formation
        - Presence of indigestible organisms or particles (TB, mineral oil, etc)
        - Cell mediated immunity (T-cells)
            - HIV decreases number of T4 cells (humoral response is B cells)

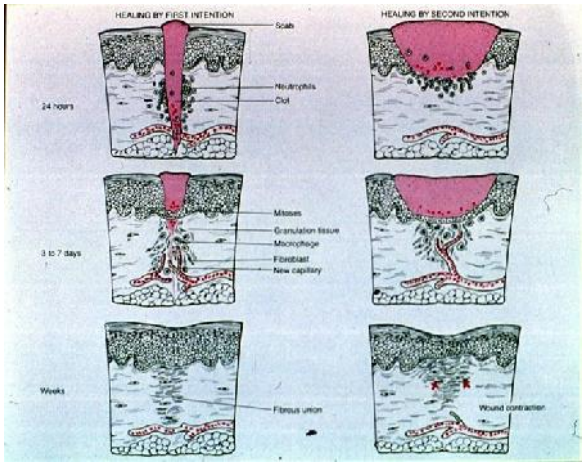


- Outcomes of Chronic Inflammation
    - Resolution/regeneration – tissue returns to normal state
    - Repair/healing – healing by CT /fibrosis/scarring
    - Can continue indefinitely (ex:// rheumatoid arthritis)

- Resolution
    - Removal of offending agent
    - Regenerative ability of cells have been destroyed
        - Labile cells – cells which continue to proliferate throughout life (gut, skin, marrow)
        - Stable cells – retain ability to proliferate, but usually don't unless stimulated (liver, kidney, pancreas, bone)
        - Permanent cells – cannot reproduce themselves after birth (neurons, cardiac, skeletal muscle)
    - Intact stromal framework – cells sit on a scaffolding, like the basement membrane



- Repair
    - Damage to parenchymal cells and stromal framework which results in replacement of nonregenerated parenchymal cells by connective tissue which, over time, produces fibrosis and scarring
    - Granulation tissue – early specialized vascular and fibrosis tissue formed
        - Grossly it looks pink and granular, histologically can see vessels and fibroblasts
    - Granulation tissue is not same as granuloma (macrophage collection)
    - Components necessary for repair
        - Angiogenesis/neovascularization of new vessels
        - Migration and proliferation of fibroblasts
        - Deposition of ECM
        - Remodeling or maturation and organization of fibrous tissue



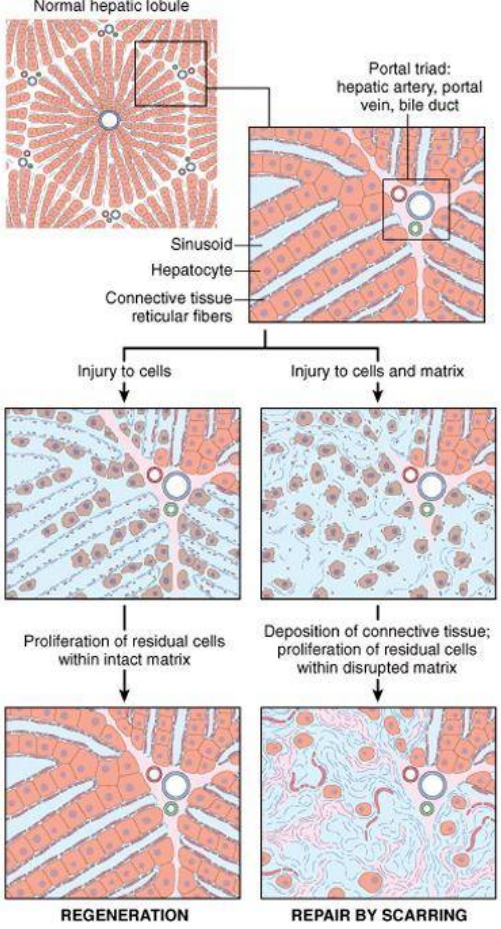
- Wound Healing
    - First intention – suture, closing the wound
    - Second intention – leave scar open to heal
        - Hole is filled with abundant granulation tissue
        - With time, wound contacts more than a wound healed via first intention. This occurs with passage of time and secondary to myofibroblasts

- Wound Strength
    - 1 week – wound strength ~ 10% strength of unwounded skin
    - Increases rapidly over next 4 weeks
    - Peaks at 3rd month, achieves 70-80% tensile strength of unwounded skin
- Additional definitions
    - Serous inflammation – outpouring of thin fluid that, depending on injury site, is derived from either blood serum or secretions of mesothelial cells lining peritoneal, pleural, and pericardial cavities
    - Fibrinous inflammation – serous fluid and plasma proteins (like fibrinogen). Seen commonly in infections of pleural cavity and pericardial sac
    - Suppurative/purulent inflammation – serous and fibrinous and pus (purulent exudate). Especially common with Staph., one of several pus producing organisms. (acute appendicitis)
    - Ulcer – local defect, or excavation of the surface of an organ or tissue, which is produced by sloughing (shedding) of inflammatory necrotic tissue. Ulceration is defined by the presence of necrotic tissue on or near the surface.

Tissue Repair

- Regeneration
- Scarring
- Combination of both

- Lots of cells proliferate during tissue repair
  - Injured tissue remnants
  - Vascular endothelial cells
  - Fibroblasts
- G1 (G0) S G2 M G1
- 3 groups of tissues
  - Labile (continuously dividing)
    - Can easily regenerate after injury
    - Contains a pool of stem cells
      - Bone marrow, skin, GI epith
  - Stable
    - Limited proliferative ability
    - Limited regenerative ability (Except liver)
    - Normally in G0
      - Liver, kidneys, pancreas
  - Permanent tissues
    - Can't proliferate or regenerate
      - Always leaves a scar
      - Neurons, cardiac



- Growth Factors
  - Important in tissue repair
    - Stimulate cell division and proliferation
    - Promote cell survival
  - Very large list, usually has GF in it (growth factor)
- ECM is anything outside the cell
  - Interstitial matrix and basement membrane
    - Sequesters water, minerals, gives cells scaffolding, stores growth factors
  - Regulates proliferation, movement, and differentiation of cells living in it
  - If you screw up ECM, you cannot regenerate scarring only

Regeneration

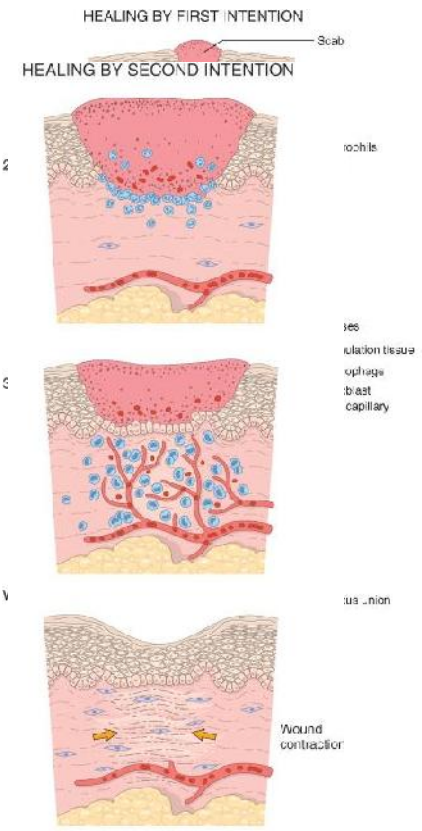
- Only occurs if residual tissue is intact
- Occurs all the time in labial tissue
    - Cells constantly being lost and replaced
    - If demand increases, supply increases readily
- Occurs limited in stable tissues
    - More like compensatory hyperplasia than true regeneration

Scarring

- Scar replaces injured tissue
    - New vessels form (angiogenesis)
    - Fibroblast proliferation
    - Synthesis of collagen (scar formation)
    - Remodeling of scar
- Timeline
    - 24h – endothelial cells start proliferation, fibroblasts emigrate
    - 3-5 days – granulation tissue present (pure granulation tissue does NOT have PMNs)
      Fibroblasts, new vessels (endothelial cells), loose matrix)
    - Weeks later – dense fibrosis (scar), scar is remodeled over time
- Summary
    - Make granulation tissue
    - Turn it into a chunk of collagen

Epithelial Healing

- First intention – small wounds, close together
    - Epithelial regeneration > fibrosis
    - Healing is fast – minimal scarring and infection
    - Tissue must be close enough together that cells can "contact" instead of growing from the basement membrane up
- 24h
    - Clot forms, Neutrophils come in
    - Epithelium begins to regenerate
- 3-7 days
    - Macrophages come in, Granulation tissue is formed (angiogenesis, fibroblasts)
    - Collagen begins to bridge incision, Epithelium increases in thickness
- Weeks later
    - Granulation tissue disappears, Collagen is remodeled
    - Epidermis is full, mature and eventually a scar forms

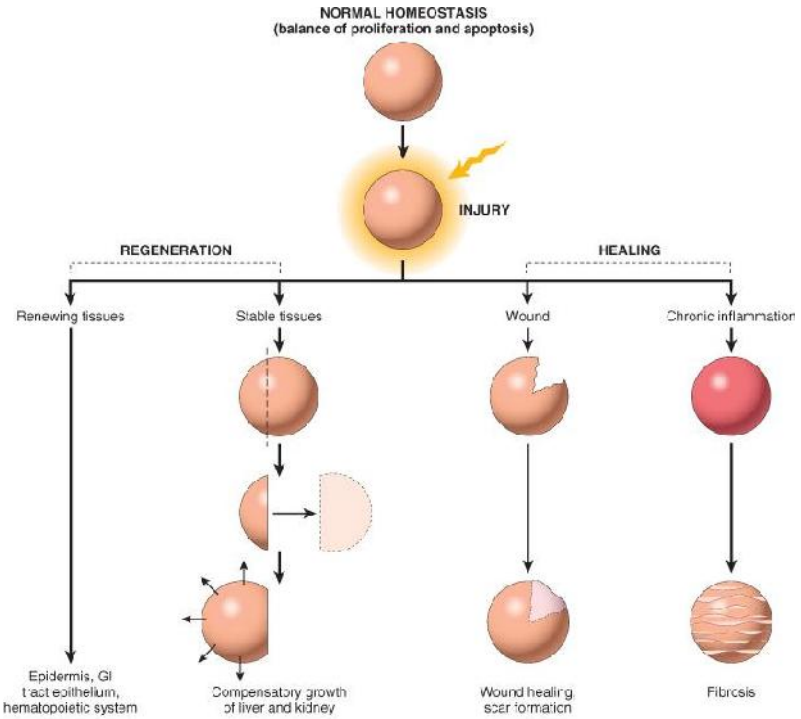


- Second intention
    - Large wounds with gaps between margins
    - Fibrosis predominates over epithelial regeneration
    - Healing is slow, more inflammation and more granulation

tissue, more scarring
    - Infarction, burns, ulcers, extraction sockets, external-bevel gingivectomies
    - Has wound contraction
- Wound Healing
    - At suture removal – 10% strength
    - Rapidly increases over next 4 weeks
    - At 3rd month, 70-80%
- Wound Degeneration
    - Extrinsic factors
        - Infection
        - Diabetes – peripheral vascular condition
        - Steroids – anti-inflammatory
    - Type of tissue injured (labial vs permanent)
    - Aberrant cell growth or ECM production
        - Keloid scar – excess collagen bundles
        - Proud flesh – excess granulation tissue

Summary

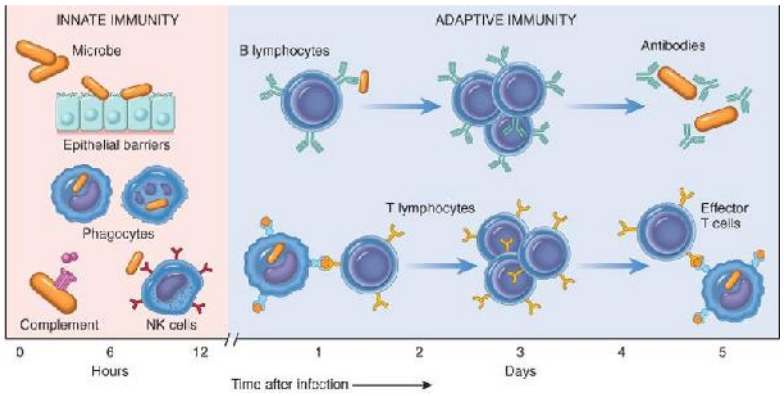
- Not all injuries result in permanent damage – some are removed almost completely
    - Usually there is some scarring
- Scar is usually good (provides resilient patch) but can be bad (can cause permanent dysfunction)



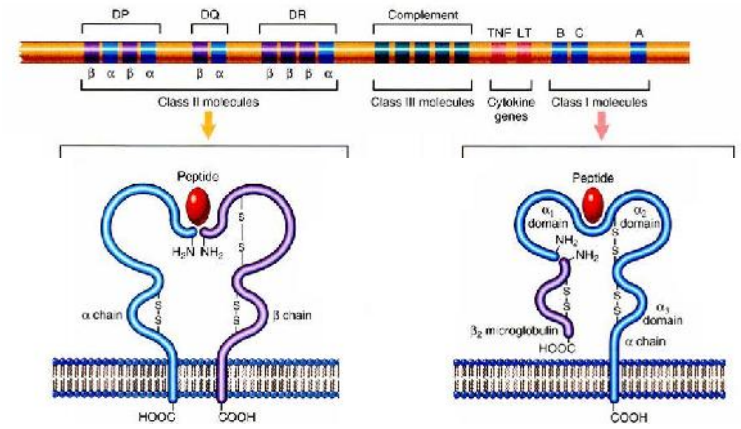
Immunology Overview

- Immunity – protection against infections
- Immune system – collection of cells and molecules that defend us against microbes
- Immune deficiencies – infections
- Immune excesses – autoimmune diseases

- Innate (natural) immunity – doesn't change over time, always present
    - First line of defense
    - Major components – epithelial barriers, natural killer cells, complement system
- Adaptive (acquired) immunity – more specific (adaptive) and powerful than innate
    - Second line of defense
    - Major components – lymphocytes, lymphocyte products
    - Two types – humoral (antibody mediated) and cellular (T-cell mediated)



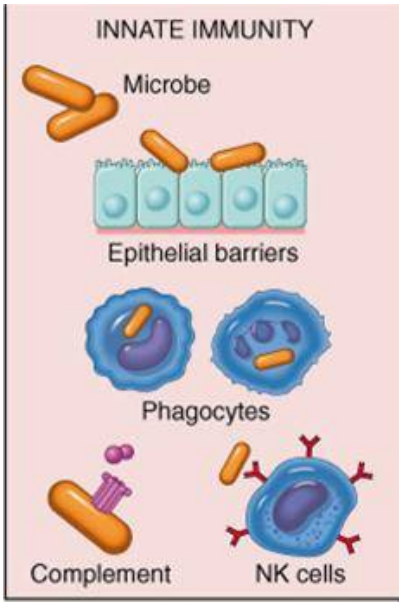
- Lymphocytes
    - Present in lymph and blood
        - T-lymphocytes develop in thymus
        - B-lymphocytes develop in bone
    - Each one has receptors for a specific antigen
        - Recognize millions of different antigens, diversity generated via:
            - Rearrangement of antigen receptor genes
            - Different joining of the gene segments
                - Gene rearrangement studies
    - Lymphoid tissues
        - Lymphocytes grow up in primary organs (thymus, marrow), then go to secondary organs searching for antigens (lymph nodes, spleen, mucosal and cutaneous lymphoid tissue)
            - Lymph node – follicle, and interfollicular areas
- T-Cells
    - Live in blood, marrow, lymphoid tissues
    - Helps other cells do their job (CD4+) and kills stuff (CD8+)
    - T-cell receptor (TCR) complex recognizes antigens, binds them and sends a signal to the T-cell
        - Antigens must be displayed by other cells AND bound to an MHC receptor
    - Helper T-cells (CD4+) – help B-cells make antibodies, help macrophages eat bugs
    - Cytotoxic T-cells (CD8+) – kills virus-infected cells and tumor cells
- MHC – major histocompatibility complex
    - Gene collection on chromosome 6, 3 regions (I, II, and III), highly polymorphic
    - Gene products – class I, II, and III molecules (and other stuff)
- MHC I
    - Encoded by 3 loci – HLA-A, HLA-B, HLA-C



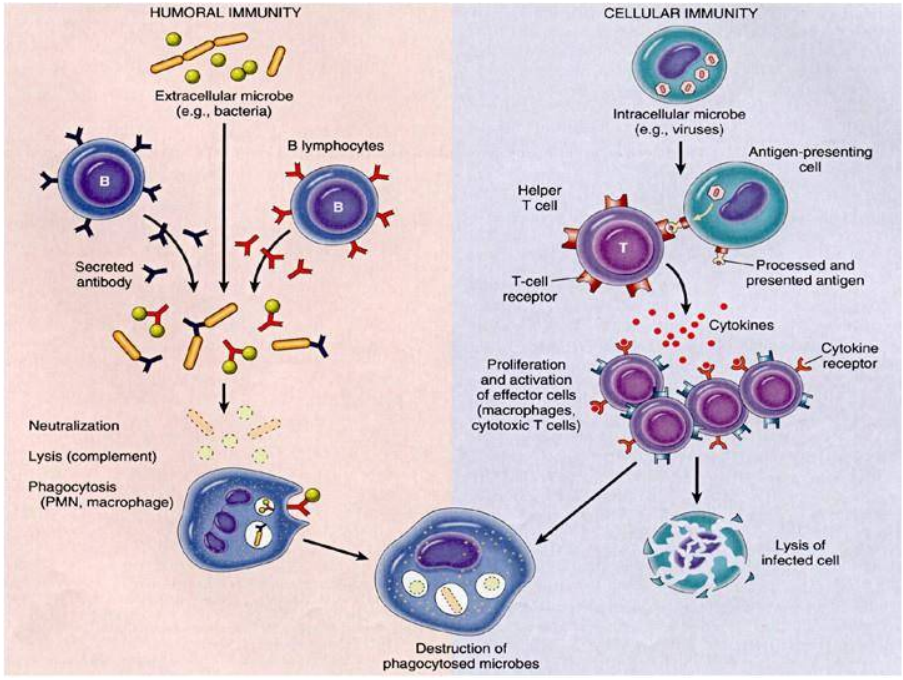
    - In all nucleated cells
    - Display antigens within the cell (ex:// viral antigens) to CD8+
- MHC II
    - Encoded by 3 loci – HLA-DP, HLA-DQ, HLA-DR
    - Display extracellular antigens (ex:// bacterial antigens cell has phagocytosed) to CD4+
    - Present mainly on antigen presenting cells
- B-lymphocytes
    - Line in marrow, blood, lymphoid tissue
    - Basic function – make antibodies (immunoglobulin)
    - B-cell receptor complex recognizes antigens, binds them, and sends signals to T-cells
    - Antigens can be free and circulating (don't have to be bound to MHCs or displayed by other cells) and are still recognized
- Natural Killer Cells
    - Part of innate immunity (NOT adaptive)
    - Kills infected/damaged cells
    - Does not have highly variable receptors like B and T cells
    - Can recognize free/circulating antigens (don't have to be MHC bound or displayed on other cells)
- Antigen presenting cells
    - Dendritic cells
        Present all over the body (skin, lymph nodes, organs) and have fine cytoplasmic projections
        Capture bug's antigens, present to B and T cells
    - Other APCs
        Macrophages eat bugs and present antigens to T-cells (activates more macrophages)
        B-cells present antigens to CD4+ T-cells, which tell plasma cells to make antibodies
- Effector Cells
    - Eliminate infections
        Types of effector cells – natural killer cells, plasma cells, CD4+ and CD8+, macrophages, other leukocytes (ex:// neutrophils)

Immune Responses

- Primary barriers – skin, mucosa
- Innate immune system – phagocytosis, cytokine activation, complement, activate adaptive immune system
    - Capturing/displaying antigens – dendritic cells in epithelium capture bug antigens, bring to lymph nodes
    - APCs in lymph nodes eat antigens, display them via MHC II receptors to T-cells
    - B-cells in lymph nodes recognize antigens
    - Antigens/molecules produced during innate immune response trigger proliferation and differentiation of B and T-cells

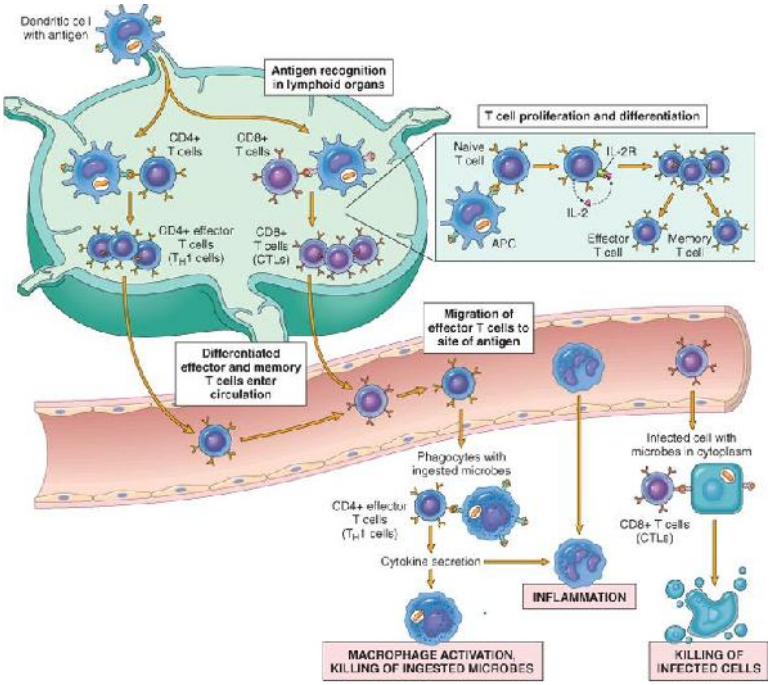


Cell-mediated immunity

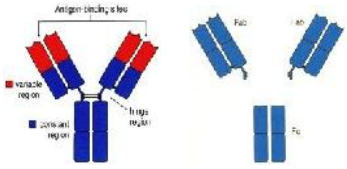


- Naïve T-cells activated via antigens and co-stimulators in lymph nodes
- Then proliferate and differentiate into effector cells, pursue finding specific antigen
- CD4+ help macrophage eat
- CD8+ kill infected cells directly
- All steps cytokine dependent

- Cytokines
  - Polypeptides that:
    - Help leukocytes grow and differentiate
    - Active T and B-cells and macrophages
    - Help leukocytes communicate
    - Recruits neutrophils
  - Made my lymphocytes and macrophages (ex:// TNF, interleukins, interferon gamma)
- T-cells
  - CD4+
    - T_H1 – activate macrophages, cause B-cells to release Ab
    - T_H2 – active eosinophils, cause B-cells to release IgE
      - Go to site of infection and, with help of macrophages and cytokines, do their thing
  - CD8+
    - Cytotoxic T-cells – kill cells that have microbes in their cytoplasm

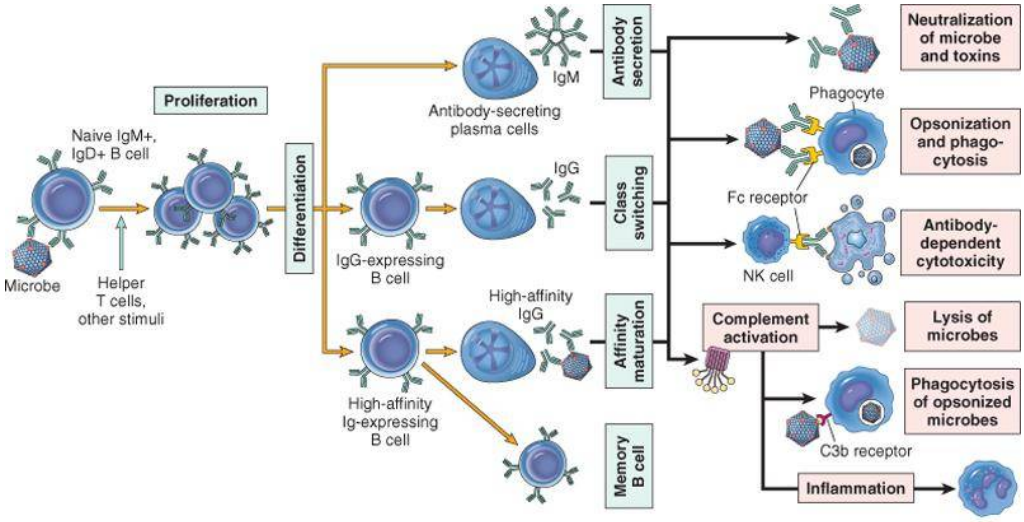


Humoral Immunity

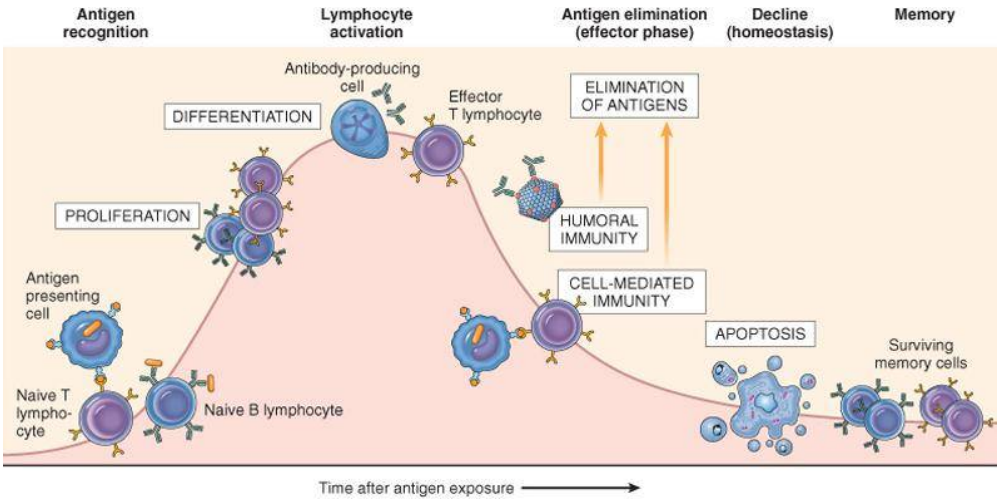


- B-cells get activated by exposure to antigens (sometimes from CD4+)
  - Differentiate into plasma cells, make antibodies
- Antibodies
  - Y-shaped glycoprotein
    - 2 light chains (κ or λ), 2 heavy chains (α, γ, δ, ε, or μ)
  - Constant regions of heavy chains form Fc fragment that binds APCs and defines isotype (ex:// IgA, IgE)
  - Variable regions of both chains forms Fab fragments that binds antigen and defines idiotype
  - Opsonize bugs so they can't do anything, makes them easier to phagocytose (macrophages and neutrophils have receptors for Fc portion of IgG)
  - Activate complement system

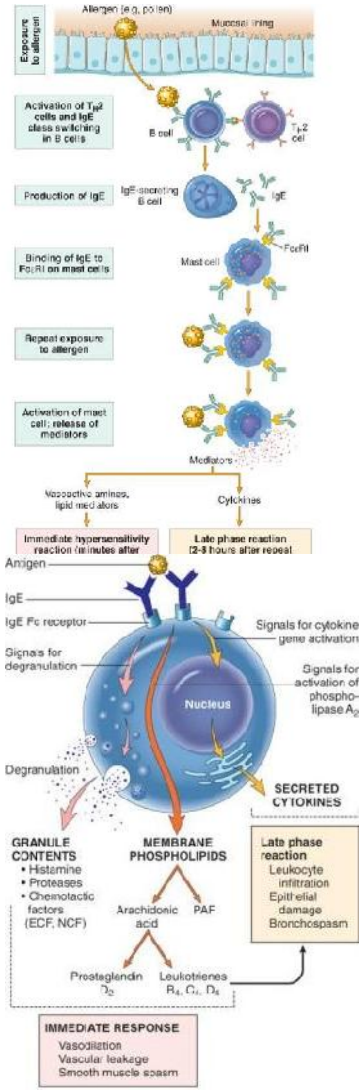
- Complement
    - 20 plasma proteins (C1, C2, etc) that punch holes into cells
    - Can be activated via – antigen-antibody complexes, bacterial LPS, bugs with mannan on their surfaces
    - Activation proceeds in a cascade fashion, with end results – cell lysis, chemotaxis, opsonization



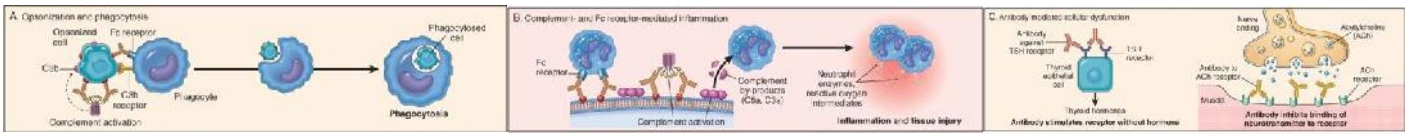
- Immunologic Memory
    - Most effector lymphocytes perish after combating infection
    - A few memory cells live on for years
        - Expanded pool of antigen-specific lymphocytes
        - Respond faster, better than naïve cells
        - Vaccines depend on these guys



Hypersensitivity Reactions

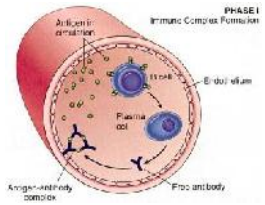


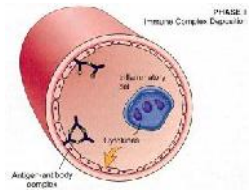
- Antigens that initiate hypersensitivity reactions – bugs, environment, self antigens
    - Immune system is triggered and maintained inappropriately
        - Hard to eliminate stimulus or stop once it starts → often chronic/debilitating, hard to treat
- Type I Hypersensitivity – Allergy ("immediate")
    - Antigen (allergen) binds to IgE on surface of mast cell → mast cell releases mediators → vessels dilate, smooth muscle contracts, inflammation persists
    - Allergens are eaten/inhaled, stimulate T_H2 production
        - T_H2 secretes cytokines
            - IL-4 stimulates B-cells to make IgE
            - IL-5 stimulates eosinophils
            - IL-13 stimulates mucous secretion
        - Mast cells bind IgE, allergen bridges IgE on mast cell, mast cell degranulates
    - Mast cells secrete
        - Granule contents – histamine, chemotactic factors
        - Membrane phospholipid metabolites – prostaglandin D_2, leukotrienes
        - Cytokines – TNF, interleukins, IL-13
            - Immediate – vasodilation, vascular leakage, smooth muscle spasm, granule contents, prostaglandins, leukotrines
            - Late phase – inflammation, tissue destruction, cytokines
    - Local reactions – skin itching, hives, diarrhea, bronchoconstriction
    - Anaphylaxis – itching, hives, erythema, bronchiole constriction, wheezing, laryngeal edema, hoarseness, obstruction, vomiting, cramps, diarrhea, shock, death
- Atopy – predisposition to allergic reactions
    - Atopic patients – elevated IgE, more T_H2 cells
    - Candidate genes
        - 5q31 – lots of cytokine genes here
        - 6p – close to HLA complex
- Type II Hypersensitivity – Antibody mediated
    - Antibodies bind to antigens on cell surface, macrophages phagocytose cells, complement is activated, inflammation harms tissue and cells die
    - Autoimmune disorders, hemolytic anemia
        - Antibodies bind to cell surface and one of 3 things happen

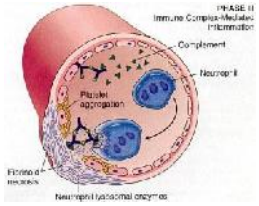


    - Graves disease – antibodies stimulate release of hormones
    - Myasthesia – antibodies block hormones from receptors

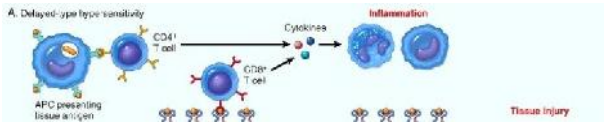
- Type III Hypersensitivity – immune complexes
    - Ab bind to Ag forming complexes, get stuck in vessels, stimulate inflammation necrosis
        - Serum sickness, arthus reaction
    - Systemic – complexes formed in circulation, deposited in organs serum sickness
        - Complexes lodge in kidney, joints, small vessels – fever, joint pains, proteinuria
    - Local – complexes formed at site of antigen injection, precipitate at injection site – arthus reaction
        - Inject antigen into skin of previously immunized person, pre-existing antibodies form complexes with antigen, precipitate at site of injection – edema, hemorrhage, ulceration
    - Complexes cause inflammation via complement
        - Attracts/activates neutrophils and monocytes, which release PG, tissue-dissolving enzymes, etc
        - Makes vessels leaky
        - Activate clotting system, causing microthrombi
            - Vasculitis, glomerulonephritis, arthritis, other –itises
    - Complement
        - C3b – promotes phagocytosis
        - C3a, C5a – increases permeability (anaphylaxis)
        - C5a – chemotactic for neutrophils, monocytes
        - C5-9 – membrane damage, cytolysis



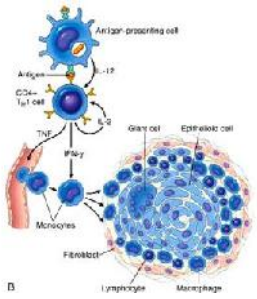




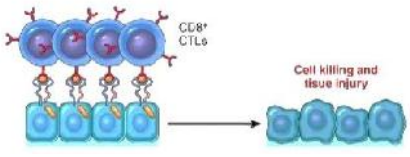
- Type IV hypersensitivity – T-cell mediated
    - Activated T-cells
        - Release cytokines that activate macrophages
        - Kill cells directly



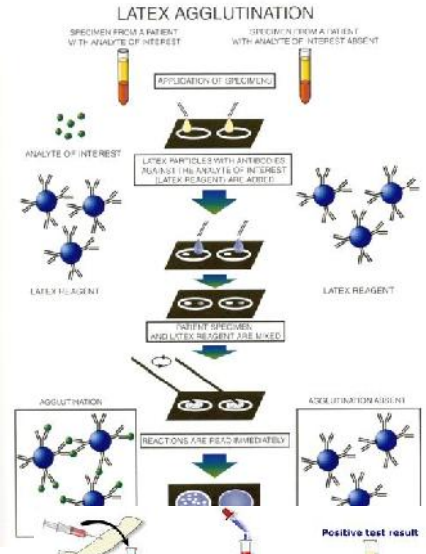
    - Normally useful against intracellular infection, can cause inflammation, cell destruction, granuloma formation
    - Delayed-type hypersensitivity (DTH) – CD4+ cells secrete cytokines, macrophages come and kill cells
        - APC presents antigen to CD4+ T-cell, T-cell differentiates into effector and memory T_H1 cells
            - Patient exposed to antigen 2nd time – T_H1 cells come to exposure site, release cytokines that activate macrophages and increase inflammation
                - Macrophages eat antigen, excessive inflammation and tissue damage
            - Ex:// mantoux test for TB – see reddening, induration peak at 1-3 days
        - Prolonged DTH can lead to granulomatous (collection of epithelioid macrophages) inflammation
            - Perivascular CD4+ replaced by macrophages, activated look “epithelioid”, can sometimes fuse into “giant cells”



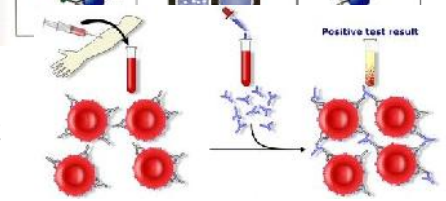
    - Direct cell toxicity – CD8+ cells kill targeted cells
        - CD8+ recognize antigens on cell surface
            - T-cells differentiate into cytotoxic T-lymphocytes (CTL) which kill antigen-bearing cells like transplanted organ cells, pancreatic islet cells (type I diabetes)
                - CTLs normally kill viruses and tumor cells



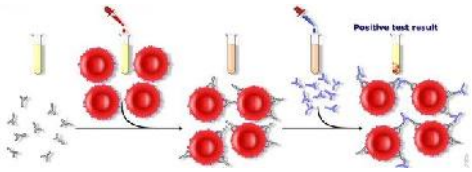
Imin Lab Tests



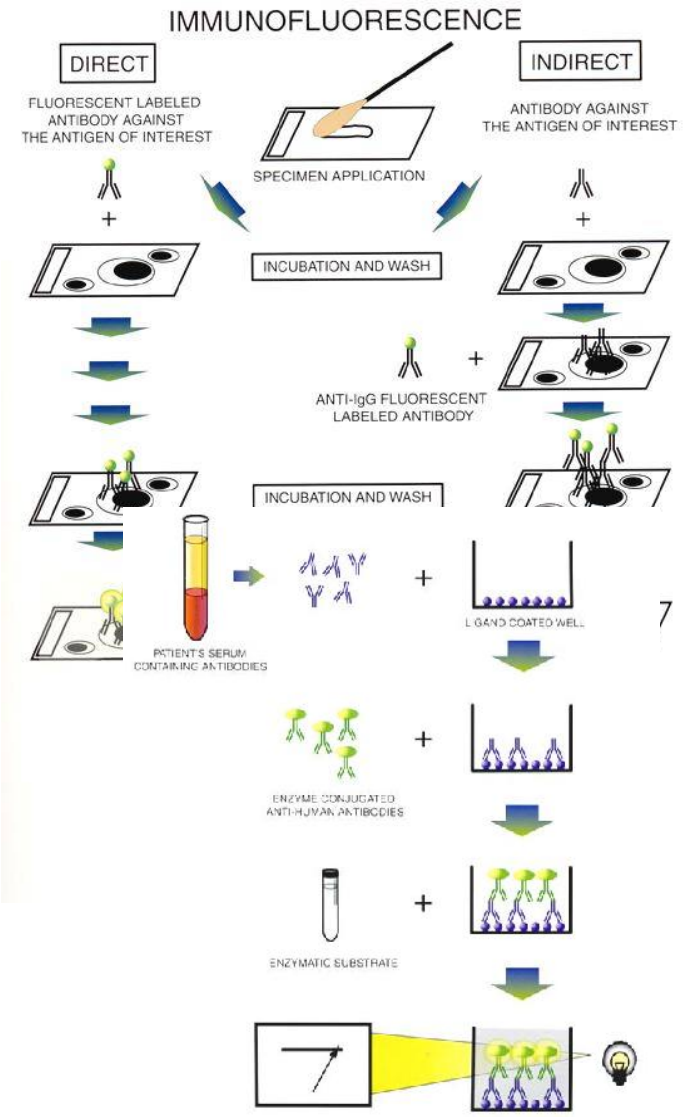
- Agglutination reactions
    - Detection of Ag or Ab in patient specimen
        - Blood typing, testing for antibodies to infectious agents, testing for hemophilus influenza type B capsular antigen in CSF
    - Use particles coated with Ab or Ag, add patients serum (containing Ag or Ab), see if particles clump
        - Clumping = patient has antibody/antigen
- Direct antiglobulin test (aka direct coombs test)
    - Detection of Ab or C' in patient's RBC
        - Performed in patients with hemolytic anemia
    - Use patients RBC coated with Ab, add anti-human globulin (AHG, aka coomb's reagent), look for agglutination
        - Clumping = patient RBC coated with antibody and/or complement



- indirect antiglobulin test (aka indirect coombs test)
    - detection of antibodies to RBC antigens
    - performed as part of pre-transfusion screening
        - antibody screen, checking for cross match
    - use patient serum with Ab, add donors RBC coated with Ag, add anti-human globulin, look for agglutination
        - clumping = patient has an antibody to donor (or reagent) RBCs

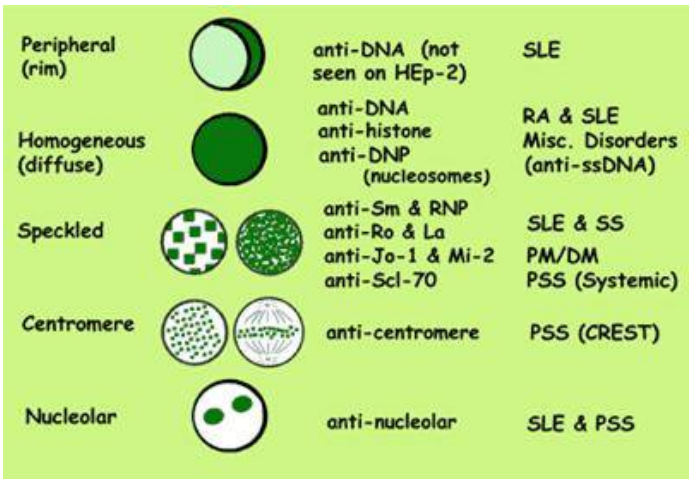


- Immunofluorescence
    - Detection of a specific antigen in specimen
        - ex:// detection of bacterial organisms, detection of Ab-Ag complexes



Direct Method	Indirect Method
Fix specimen on slide Add Ab specific for the desired Ag Look for fluorescence	Fix specimen on slide Add Ab specific for desired Ag Add second Ab Look for fluorescence

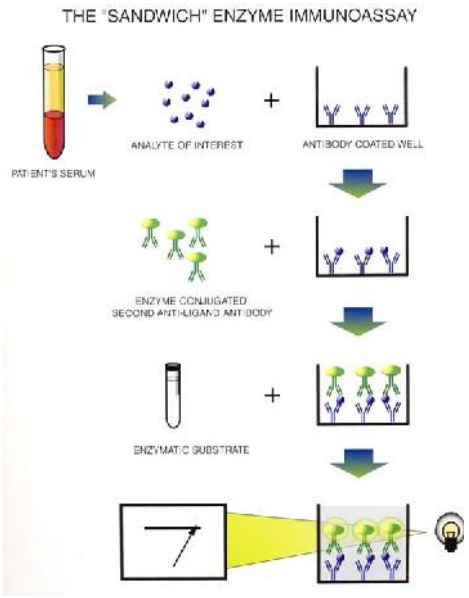
- fluorescence = patient has the antigen



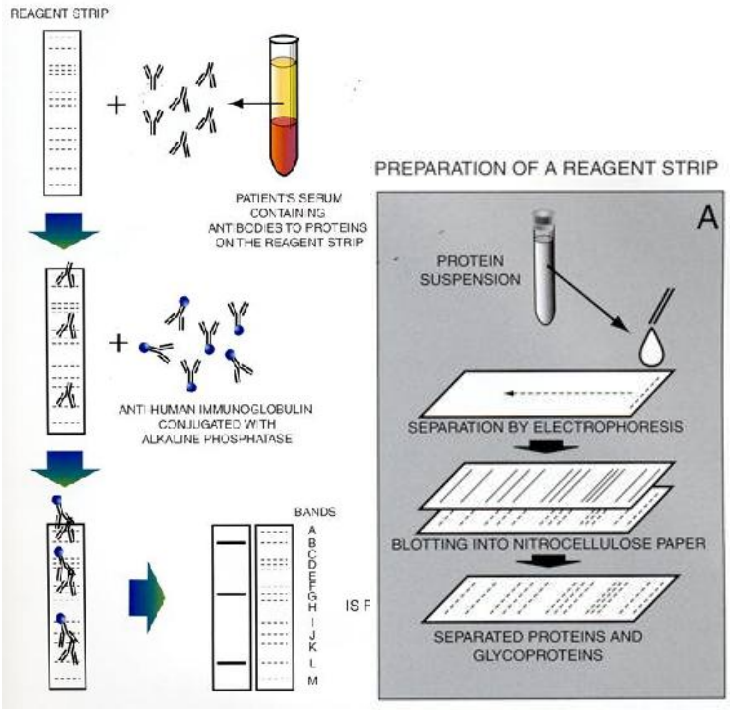
- ELISA (enzyme linked immune-sorbent assay)
    - Detection of Ab in patient specimen

Home pregnancy tests, HIV tests, tests for some coagulation factors, cytokines, autoantibodies

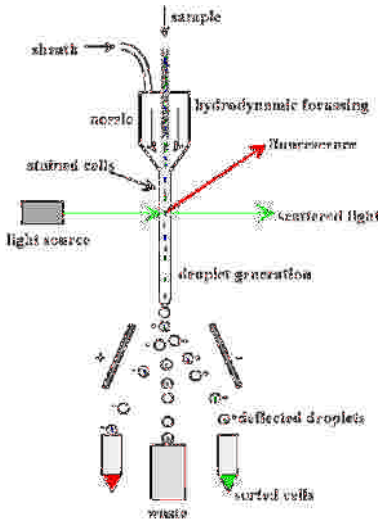
- Add patient specimen well coated with ligand, add AHG with enzyme attached, add substrate, measure color change
  - Color change = patient has antibody
- ELISA Variations
  - Sandwich immunoassay
    - Detects antigen instead of antibody
    - Coat well with antibody, rest is like ELISA
  - Radioimmunoassay
    - Detects antibody or antigen
    - Detector is a radioactive substance
    - Otherwise like ELISA or sandwich assay

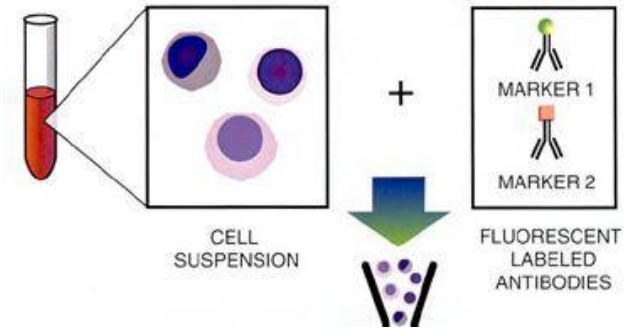


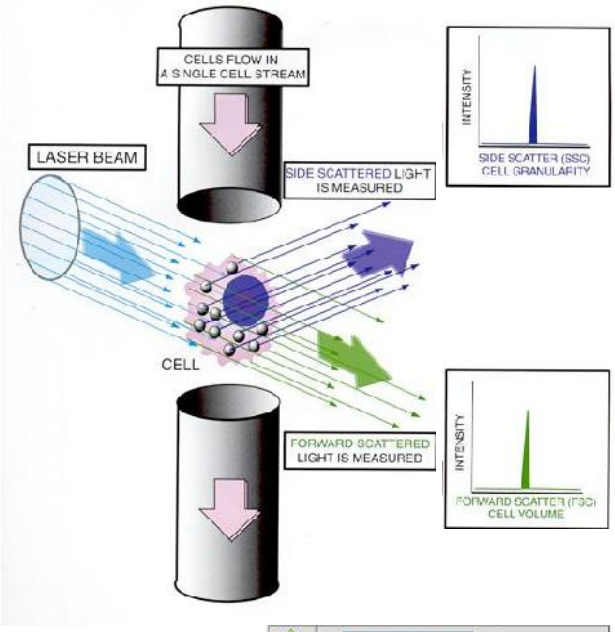
- Western Blot
  - Detection of antibodies in patient specimen
    - Most common example – HIV test
  - Make a protein suspension of the target of the antibody you're looking for (ex:// HIV)
    - Electrophorese the suspension into a little gel strip
    - Apply patient's specimen (containing Ab) to the strip
    - Add AHG that has an enzyme attached
    - Add substrate and look for bands
  - Bands on strip = patient has antibodies to corresponding proteins
    - Enough bands and the patient can be considered "positive"

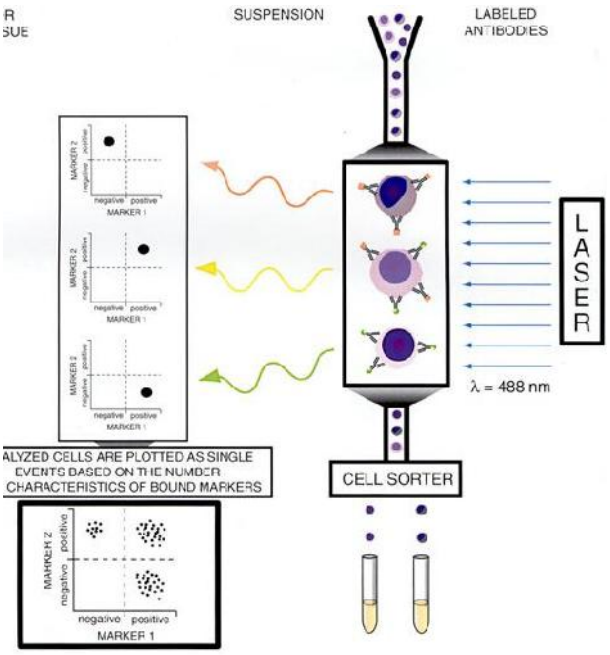


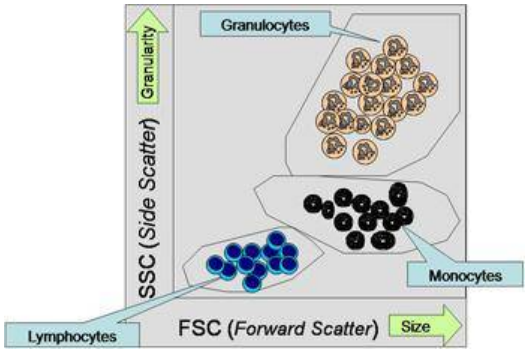
- Flow Cytometry
    - Characterization of cell size, complexity, antigens
      Diagnosis of leukemia and lymphoma, determination of CD4/CD8 counts in HIV positive patients
    - Complicated – combine size, complexity, and antigen expression data to come up with meaningful cell descriptions

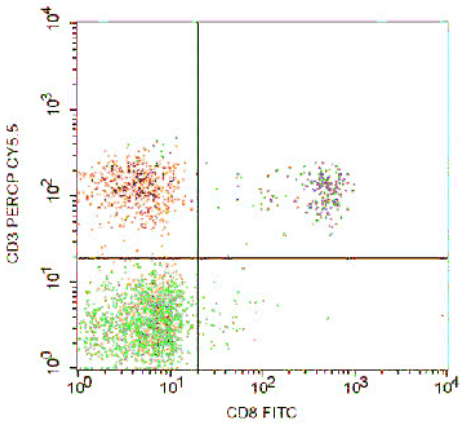


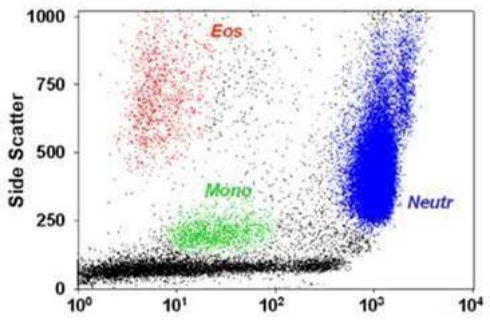












Health Care Maintenance

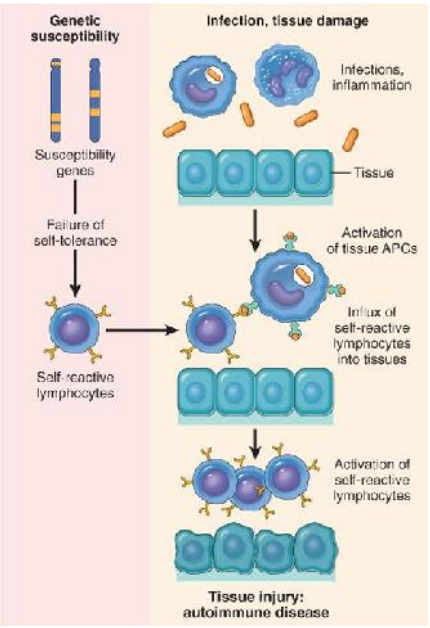
- Periodic Health Exam
    1. Address any symptoms/conditions/concerns
    2. Determine risk factors
    3. Address immunizations and preventative medications
    4. ID and perform most important elements of physical exam
    5. Recommend appropriate screening
    6. Education accordingly
- Periodic physical exam more appropriate than annual
    - If risk changes, exam may be warranted
    - Not designed as a screening test
    - Whenever possible, consider high priority interventions
- Good screening tests
        - Common problems
        - Pre-symptomatic population
        - Acceptable to patients
        - Readily treatable – improved survival and/or quality of life
        - Effective – high sensitivity – specificity positive in, sensitivity negative out (SpPIn, SnNOut)
        - Cost-effective
    - Criteria for screening
        - Disease must cause major harm
        - Treatment available
        - Must have a "latent" phase
        - Treatment during latency must be better
        - Reasonable cost and disease impact justifies cost
- Abbreviations
    - COPD – chronic obstructive pulmonary disorder
    - HTN – hypertension
    - CCD – chronic coronary disease
- Most important elements of a physical exam
    - Foot pain exam/evaluation
    - Evaluate HTN, CCD, COPD
    - Signs of liver disease
    - Head/neck/oral exam
    - Prostate, skin
- CAGE – score >0 may indicate alcohol dependence
    - Ever felt you needed to cut down on drinking?
    - People annoyed you by criticizing your drinking?
    - Ever felt guilty about drinking?
    - Needed an eye-opener drink in the morning?
- AUDIT – score >5 is hazardous

Motivational Interviewing

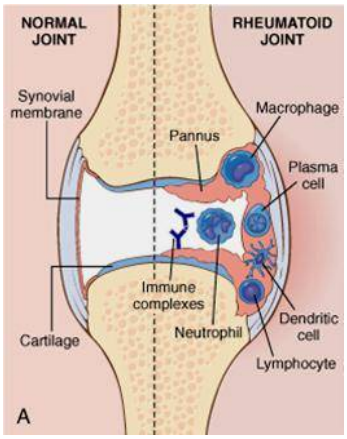
- A patient centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence
    - As I hear myself talk, I learn what I believe
- 4 principles
    - EDRS – Empathy, develop discrepancy, roll with resistance, support self-efficacy
        Clinicians with empathy predicts a 66% increase in behavioral change after 6 months
    - OARS – Open ended questions, affirmative statements, reflective listening, summarizing
    - DARNCs – desire, ability, reasons, need, commitment
- The more resistance is displayed, the less inclined patient is to change – dig deeper to motivate patient
    - Causes of resistance – moving too fast, taking control away from patient, not appreciating patient's perspective, meeting force with force, setting goals for your patient instead of with your patient
- Dealing with resistance
    - Emphasize past successes (Even if small), success involves patient believing in self, end reflective statements with a period instead of question mark, believe in possibility of change
- Developing change plan
    - Set concrete, behavioral goals
    - Articulate reasons for change
    - ID specific steps to reach goals
    - ID barriers
    - Articulate plan for managing barriers
    - Summarize plan
    - Set up clear follow ups to track for success and adjustments if needed
    - DO NOT GIVE ADVICE (patient's goals, NOT your goals)
- Benefits of motivational interviewing
    - Increased partnerships with patients
    - Decreased power struggles and frustrations with patient visits
    - Improved adherence and outcomes in subsequent treatment for patients

Immune Diseases

- Tolerance – unresponsiveness to an antigen
- Self-tolerance – unresponsiveness to self-antigens
    - In generating B and T cells, some will react against self-antigens
        - Two ways of dealing with this:
            - Central tolerance - auto-reactive B & T cells deleted during maturation
                - Apoptosis in thymus and marrow
                - Process not perfect (some get out)
            - Peripheral tolerance – auto-reactive B and T cells muzzled in periphery
                - Some become anergic (unreactive)
                - Some suppressed by regulatory T-cells
                - Some undergo apoptosis when activated
- Autoimmunity – immune reaction against self
    - Cause is unclear – may be a genetic predisposition activated by environmental factors
    - Self-tolerance breaks down, causing disease. Two primary reasons
        - Genes
            - HLA-DR4 - ↑ risk of rheumatoid arthritis
            - HLA-B27 - ↑ risk of ankylosing spondylitis
        - Environmental triggers
            - Exposing hidden self-antigens
            - Activate antigen presenting cells
            - Mimic self-antigens



- Lupus
    - Typically young female with butterfly rash
    - Multisystem, but unpredictable (remitting) symptoms
    - Antinuclear antibodies (however, also found in other diseases)
        - Anti-RBC, -lymphocyte, -platelet, and –phospholipid antibodies may also be present
    - Genetic predisposition triggered by environment
    - Antoantibodies for immune complexes, cause destruction, phagocytosis of cells
        - Renal failure (complex in glomeruli, can give the glomerulus a “wire loop” appearance by thickening the walls), epidermis (butterfly rash), CNS focal neurologic deficits, arthritis, pericarditis and endocarditis (libman-sacks lesions, almost always on BOTH sides of the valve)
    - What a dentist might see – butterfly rash, fatigue, light sensitivity, headaches, seizures, psychiatric problems, pleuritic chest pain, unexplained fever, oral lesions (nonspecific red-white, erosive) vasculitic rash (type III), hitch hiker’s thumb
        - Variable symptoms, very rare that patients die within a few months
        - Most patients relaps, remit over many years, acute flare ups controlled via steroids, 80% survival over 10 years
        - Most common cause of death is renal failure
    - Discoid lupus – skin involvement only, but may develop into systemic lupus



- Rheumatoid arthritis
    - Symmetric, mostly small-joints (can include knees, shoulders, elbows), systemic systems (skin, heart, vessels, lungs, hand features), chronic synovitis with pannus formation (synovial cell proliferation, inflammation, granulation tissue)
    - Rheumatoid factor
        - Circulating IgM antibody, directed against self-IgG
            - Forms IgM-IgG complexes, which deposit in joints and cause trouble – present in 80% of patients
    - Cytokines (especialy TNF) cause damage
    - Genetic predisposition triggered by infection, self-antigens, etc, activates T-cells
        - T-cells release cytokines – most important being TNF
            - Activate macrophages (causing destruction)
            - Cause B-cells to make antibodies against the joint
            - Cytokines cause inflammation, tissue damage
        - Lots of lymphocytes present in histological slides

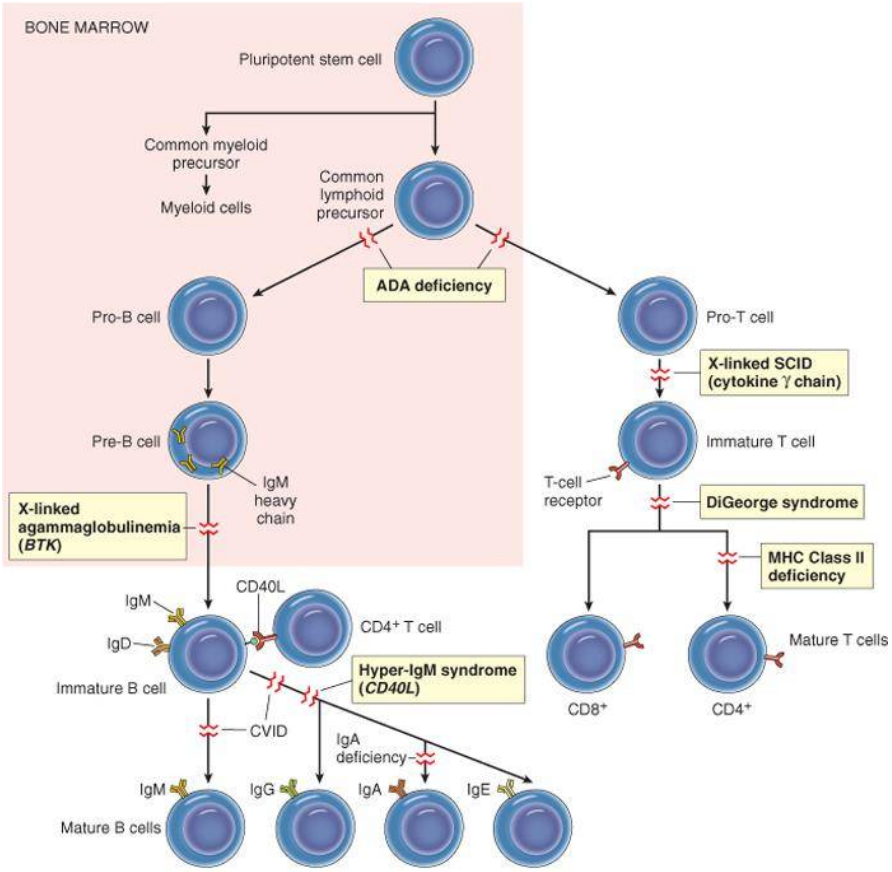
    - Symptoms – weakness, malaise, fever, vasculitis, pleuritis, pericarditis, lung fibrosis, eye changes, rheumatoid nodules in forearms
        - Female patients with aching, stiff joints especially in the morning (improves with movement, unlike osteoarthritis), symmetric joint swelling
        - Fingers – ulner deviations, swan-neck deformities, boutonneire deformities
    - Variable prognosis, few patients stabilize, most patients have chronic course with progressive destruction and disability, shortened lifespan 10-15 years, treat with steroids, anti-TNF agents
- Sjogren's syndrome
    - Inflammatory disease of salivary, lacrimal glands – dry eyes, dry mouth
    - T-cells react against self-antigens in gland, destroying it
    - Increased risk of lymphoma
        - CD4+ cells attack self-antigens in glands
            - Antibodies are present, but probably not cause of tissue injury
                - ANAs, RF, anti-SS-A, anti-SS-B?
                - Viral trigger?
                - Genetic predisposition?
    - Symptoms – enlarged salivary and lacrimal glands, marked inflammation and gland destruction, 40x increased risk of lymphoma
    - Systemic disease – fatigue, arthralgia/myalgia, Raynaud phenomenon (1 or more fingers (periphery) turns white), vasculitis, peripheral neuropathy, often the patient has other autoimmune diseases too
    - Things a dentist might see
        - 35-45 year old female, enlarged salivary glands, Raynaud phenomenon, keratoconjunctivitis sicca (dry eyes), oral changes
            - Xerostomia, mucosal atrophy, candidiasis, mucosal ulceration, dental caries, taste dysfunction
    - Treatment is mostly supportive and symptom based
        - Dental – adequate hydration, scrupulous dental hygiene, cholinergic agents (stimulate saliva release), frequent dental exams
        - Ocular – lubricating solutions for eyes, surgical procedures
        - Systemic – steroids, other immunosuppressive drugs

- Scleroderma (systemic sclerosis)
    - Excessive fibrosis throughout body (skin, viscera)
    - Claw hands, mask-like face
    - Microvascular disease also present
    - Diffuse and limited types
        - CD4+ accumulates for some reason, T-cells release cytokines that activate mast cells and macrophages – release fibrogenic cytokines while B-cells also activate but don't do anything (diagnostic antibody – anti-scl 70)
            - Cause of microvascular disease unknown
            - Best way to look for antibodies if fluorescence (FLANA)
    - Symptoms
        - Skin – diffuse, sclerotic atrophy. Fingers first
        - GI – "rubber-hose" lower esophagus
        - Lungs – fibrosis, pulmonary hypertension
        - Kidneys – narrowed vessels, hypertension
        - Heart – myocardial fibrosis
    - Scleroderma (limited type)
        - Mild skin involvement – face, fingers
        - Involvement of viscera occurs later
        - Also called CREST syndrome
            - Calcinosis
            - Raynaud syndrome
            - Esophageal dysmotility
            - Sclerodactyly
            - Telangiectasia
        - Benign course
    - Scleroderma (diffuse type)
        - Initial widespread skin involvement
        - Early visceral involvement
        - Rapid course
    - Things a dentist might see
        - Female 50-60, Raynaud syndrome, stiff claw-like fingers, mask-like face, difficulty swallowing, dyspnea, chronic cough, difficulty getting dentures in
    - Prognosis
        - Stead, slow downhill course over many years
        - Limited scleroderma may exist for decades without progressing
        - Diffuse scleroderma is more common, has worse prognosis
        - Overall 10-year survival = 35-70%

Primary Immune Deficiencies

- Primary type – inherited
- Secondary type – to infection, immunosuppression, etc

- Patients more susceptible to infections, cancer
  - Types of infections vary
    - Ig, complement, phagocytic cell defects – bacterial infections
    - T-cell defect – viral and fungal infections
- Primary immune deficiencies – rare, genetic, can affect any part of human immune system
  - Adaptive – humoral or cellular
  - Innate – complement, phagocytes, NK cells
  - Typical patients – infant with recurrent infections



Disease	Transmission	Defect	Clinical Stuff
X-linked agammaglobulinemia	X-linked Affects males only	Pre-B cells don't differentiate Patients have no immunoglobulin	Presents at 6 months - Material Ig gone Recurrent bacterial infections Treat via intravenous pooled human Ig
Common variable immunodeficiency	Affects male and females equally	Group of disorders characterized by defective antibody production Basis of Ig deficiency is variable and often unknown	Presents in teens or twenties Patients more susceptible to infections, but ALSO autoimmune disorders and LYMPHOMA
Isolated IgA deficiency	Most common of all primary immune deficiencies Unknown cause	Most patients are asymptomatic	Some patients get recurrent sinus/lung infections/diarrhea (IgA major Ig in mucosal secretions) Possible anaphylaxis following blood transfusions (patients have antibodies against IgA, but IgA in transfusion blood) Increased incidence of autoimmune disease
Hyper IgM syndrome	X-linked (most cases)	Patients make normal (or increased) amounts of IgM, but can't make IgA, IgG, or IgE Patients also have defect in cell-mediated immunity	Patients have recurrent bacterial infections and infections with intracellular pathogens (pneumocystis jiroveci)
DiGeorge syndrome		Developmental malformation affecting 3rd and 4th pharyngeal pouches Thymus doesn't develop well Patients don't have enough T-cells	Infections – viral, fungal, intracellular pathogens Patients may also have parathyroid hypoplasia Treatment via thymus transplant
Severe combined immunodeficiency	Lots of very different genetic factors Half of all cases are X-linked	Group of syndromes with both humoral and cell-mediated immune defects	Patients get all kinds of infections Treatment – bone marrow transplant

Transfusion Medicine

- How to make antigens
    - Start with protein precursor
        - Add fucose to make H-Ag
            - Add N-acetylgalactosamine to H-Ag to make A-Ag
            - Add galactose to H-Ag to make B-Ag
- Almost everyone has H gene (codes for enzyme that makes H-antigen)
- ABO genes – everyone has 2 genes (6 possible genotypes)
    - A and B genes code for enzymes that make A and B antigens
    - O is where there is no product

Blood Type	O	A	B	AB
% of population	42%	40%	12%	6%

- We have antibodies for antigens we don't have
    - Anti-A antibodies lyse A red cells
    - Important for blood transfusion

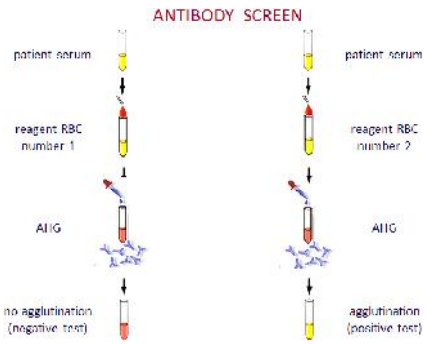
- Most important antigen – antigen D
    - Called "Rh" because discovered in rhesus monkeys
- 2 alleles – D and d – DD or Dd gives Rh+, dd gives Rh-
- Antibodies are ACQUIRED (unlike ABO system)
    - To make anti-D you must be Rh- AND be exposed to Rh+
    - Donor and recipient are tested for D-antigen

- There are around 42 other systems, but they are much less important. Most of their antibodies are also acquired, so only need to worry for blood transfusions or pregnancy

- Whole blood – RBC, WBC, platelets, plasma – used for massive hemorrhage
    - Red cells – RBC, a few WBC, few platelets, few plasma – used for low hemoglobin
        - Leukocyte-reduced red cells – RBC, no WBC, rare platelets, little plasma – used for decreased alloimmunization, used for low decreased allergic reactions
        - Frozen red cells – RBC, few WBC – used for storage of rare blood types
    - Granulocytes – neutrophils – use for sepsis in neutropenic patients
    - Platelet-rich plasma
        - Platelets – platelets – used for bleeding due to thrombocytopenia
        - Fresh frozen plasma – plasma and coagulation factors – use for bleeding due to multiple factor deficiencies
            - Cryoprecipitate – fibrinogen, von Willebrand factor, factor VIII, IX – use for low fibrinogen, vW disease, hemophilia A, XIII deficiency
            - Factor VIII – use for hemophilia A
            - Factor IX – use for hemophilia B
            - Albumin – use for hypovolemia with hypoproteinemia
            - IgG – IvIG – use for disease prophylaxis, autoimmune disease, immune deficiency states

- Blood Testing

- Forward type – done using both anti-A and anti-B antibodies
  Patient RBC, anti-A added (or anti-B) to coat cells if antigen present, AHG added to aggregate cells coated with antibody, positive result if you can see aggregation (patient has that cell type)
- Reverse type – done using both type A and type B reagent cells
  Patient serum with antibodies, reagent cells (type A or B) added, AHG added to aggregate antibodies attached to cells, positive result if you can see aggregation (patient has antibody type)
- Crossmatch – tests donor and patient blood for reactivity
  Patient serum (with antibodies), add donor RBC, add AHG to test for compatibility, donor blood cannot be used if blood aggregates



- Dangers
  - Transfusion reactions
    - Hemolytic
      - Acute hemolytic transfusion reactions
        - Patient has ABO antibodies against donor red cells
        - Most common reason – clerical error
        - Symptoms – fever, chest pain, hypotension, hemoglobin in urine and serum
        - Labs – ↓ haptoglobin (free hemoglobin binder), ↑ bilirubin, DAT positive
        - Type and crosstype shows ABO mismatch
      - Delayed hemolytic transfusion reactions
        - Hemolysis occurs days after transfusion – usually extravascular (liver, spleen, etc)
        - Caused by antibodies binding to non-ABO antigens
        - Falling Hemoglobin after transfusion
        - Usually not severe
        - DAT positive, antibody screen IDs the antibody
    - Non-hemolytic
      - Febrile transfusion reaction
        - Caused by recipient Ab against donor WBC
        - Cytokines fever, headache, nausea, chest pain
        - Diagnosis – rule out everything else
        - Treatment – Tylenol, leukocyte reduced components
      - Allergic transfusion reaction
        - Probably host reaction to donor plasma proteins
        - Symptom – hives
        - Treatment – antihistamines
        - Anaphylaxis or other severe reactions rarely seen
  - STOP TRANSFUSION – check if right blood went to right patient, monitor vitals, send blood and urine and bag to donor bank
    Lab – checks paperwork, looks for hemoglobinuria, do a DAT, repeat ABO and Rh testing

- Other complications
    - Infections
        - Bacterial infection
            - Uncommon, but serious risk
            - Sudden fever and shock
            - Patient (and blood unit) must be tested
            - Treat with aggressive resuscitation and antibiotic therapy
        - Donor tests – HIV, HTLV, hep B and C, syphilis (even with testing can be transmitted)
        - Other transmissible infections – viruses (EBV, CMV), parasites (malaria, lyme disease)
    - Circulatory overload
        - Happens when too much blood is given too quickly
        - Symptoms – hypertension, congestive heart failure
        - Treatment – stop transfusions, give diuretics
    - Iron overload
        - Too much iron can damage heart, liver
        - Patients with chronic anemias are at biggest risk
        - Give iron-chelating agents
    - Graft vs host disease
        - Donor lymphocytes attack host
        - Most common in immunocompromised patients or patients with blood-relative donors (antigens are too similar – patient doesn't react but donor WBC react and proliferate)
        - Fever, rash, hepatitis, marrow failure
        - Usually fatal – prevent by irradiating products

- Risks
    - Bacterial infection – 1/50K (platelet transfusion), 1/500K (RBC transfusion)
    - Hep B – 1/300K
    - Hep C – 1/2M
    - HIV – 1/2M
    - Allergic reaction – 1/100, 1/20K (severe)
    - Febrile reaction – 1/200
    - Circulatory overload – 1/3K
    - Delayed hemolysis – 1/4L, 1/4M (fatal)
    - Acute hemolysis – 1/20K, 1/600K (fatal)
    - GvH disease – unknown

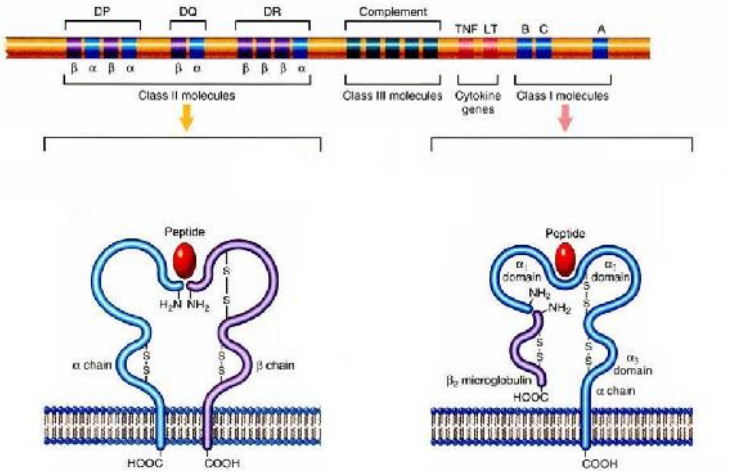
Transplant Pathology

- Transplant – moving of cells/tissue/organs from one site to another
- Graft – the transplanted organ
- Donor – person from whom graft is taken
- Host – person who receives graft
- Transplantable things – kidney, pancreas, heart, lung, liver, marrow, intestine, skin, cornea
- Problems – surgical difficulties, graft rejection, organ shortage

- Rejection – host recognizes graft as foreign, destroys it
- Autograft – within same person
- Isograft – between identical twins
- Allograft – within species
- Xenograft – between species

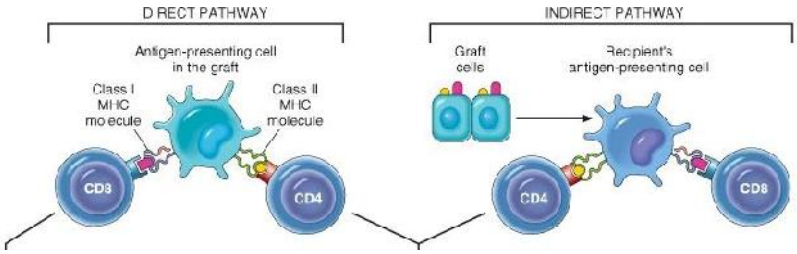
- Histocompatibility – antigenically similar to host
- Histoincompatible – antigenically different from host
- MHC class II antigens are the most important
    - ABO antigens are also important
    - Minor histoincompatibility antigens are less important

- HLA complex – gene collection on chromosome 6
    - Class I – HLA A/B/C
        - Expressed on nearly all cells
        - Present antigens to T_c cells
    - Class II – DP/DQ/DR
        - Expressed on antigen presenting cells
        - Present antigen to T_H cells
    - Class III – complement system
        - C4, C2, BF
        - C' proteins
        - TNF α and β

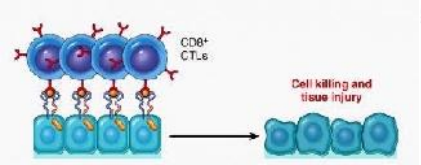


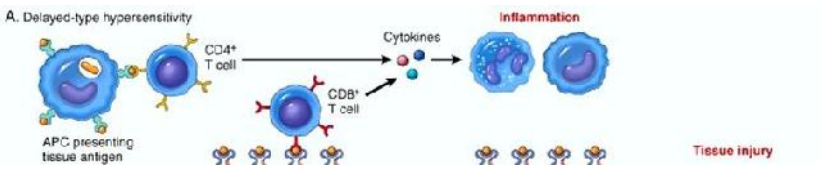
- HLA genes are inherited as a haplotype (set). One set per chromosome, and all 3 genes (per chromosome) are codominantly expressed, so 6 genes are expressed.
    - Mismatch in class I – not too big a deal
    - Mismatch in class II – big deal
    - Mismatch in class I and II – very big deal

- Graft rejection
    - Hosts have 2 pathways for recognizing which cells to kill
        - Direct pathway
        - Indirect pathway



    - T-cell mediated rejection – CD8+ and CTLs kill graft cells directly
        - There is also a delayed hypersensitivity reaction (CD4+ killing)





- Antibody mediated rejection – preformed and newly made antibodies
    - Preformed antibodies
        - Anti-HLA or anti-ABO
        - Rejection occurs immediately (acute) – antibodies form thrombosis
        - Rare these days
    - Newly made antibodies
        - Appear within days to years
        - Usually directed against graft endothelium
        - Cause damage via – helping complement kill graft cells and opsonizing graft cells
- Antibody-dependent cell-mediated cytotoxicity
    - Target cell coated with IgG
    - Effector cell (macrophage, NK cell, neutrophil) has receptors for Fc fragment
    - Effector cell binds to target cell, lyses it

- Clinical types of rejection
    - Hyperacute rejection
        - Within hours – “accelerated” is similar
        - Preexisting anti-donor antibodies
        - Rare these days
    - Acute rejection
        - Starts at about 10 days
        - Cell-mediated
    - Chronic rejection
        - Months to years after transplant
        - Humoral and cell-mediated mechanisms
        - Hard to prevent, hard to treat

- Types of organ transplants
    - Kidneys – diabetes, glomerulonephritis, congenital disorders
        - Most common transplant
        - Problems
            - Host sensitization – first graft causes creation of antibodies for all antigens in graft, so next graft is harder to find a clean match
            - Post-transplant malignancy
    - Heart – cardiomyopathy, myocarditis, congenital defects, ischemic disease
        - Must use heart-lung device
        - Problems
            - Organ shortage
            - Maintaining graft before transplant
            - Atherosclerosis
            - Post-transplant lymphoma
    - Marrow – leukemia, lymphoma
        - Finding living donor is easy, finding matches is hard
        - Massive chemo/radiation first
        - Problem – GvH disease – donor T-cells see recipient as foreign – attack skin, GI, liver
            - Treat with immunosuppressants or partially delete donor marrow of T-cells
    - Lungs – cystic fibrosis, emphysema, acute lung damage
        - Survival rate is 60% at one year
    - Liver – congenital abnormalities, end-stage liver disease (many causes)
        - Donor liver may be split (compensatory regeneration)
        - Problems with bleeding and rejection
    - Pancreas – diabetes
        - May transplant kidney at same time
        - Islet transplant alone seems to work great (transplanted into LIVER)
    - Epidermal – severe burns
        - Usually autologous
        - If burn is very severe, use allogeneic skin (frozen, more like a dressing)
        - Cannot use immunosuppressive therapy

- Xenotransplantation
    - Human organs are scarce, so other species may help
    - Solid-organ transplant hasn't worked well
    - Rejection is a major problem
        - UMN research into pig islet cells into humans
    - Xenozoonoses can be fatal

Neoplasm – mass of tissue that grows excessively even if you remove starting stimulus

Benign tumours are well differentiated (look similar to tissue of origin) while malignant tumours are poorly differentiated

If the tumour is metastatic, it is malignant

Benign tumours (usually end with –oma)

- Adenoma – glandular cells
- Leiomyoma – smooth muscle cells
- Chondroma – chondrocytes
- Papilloma – finger-like projections
- Polyp – projects upward, forming a lump
- Cystadema – has hollow space (cyst) inside

Most benign tumours have a fibrous capsule

Malignant tumours

- Carcinomas – epithelial tissue
    - Adenocarcinoma – glandular cells
    - Squamous cell carcinoma – squamous cells
- Sarcomas – mesenchymal tissue
    - Chondrosacroma – chondrocytes
    - Angiosarcoma – blood vessels
    - Rhabdomyosarcoma – skeletal muscle cells

Mixed tumours – show divergent differentiation (not to be confused with teratomas)

- Pleomorphic adenoma – glands + fibromyxoid stroma
- Fibroadenoma – glands + fibrous tissue

Confusing Terms

- Lymphoma, mesothelioma, melanoma, seminoma

Non-tumours

- Hamaratoma – mass of disorganized indigenous tissue
- Choristoma – heterotopic rest of cells

Names that seem to come out of nowhere

- Nevus
- Leukemia
- Hydatidiform mole

Tissue of origin	Benign	Malignant
Fibrous tissue	Fibroma	Fibrosarcoma
Fat	Lipoma	Liposarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteogenic sarcoma
Blood vessels	Hemangioma	Angiosarcoma
Mesothelium		Mesothelioma
Hematopoietic cells		Leukemia
Lymphoid cells		Lymphoma
Squamous epithelium	Squamous cell papilloma	Squamous cell carcinoma
Glandular epithelium	Adenoma	Adenocarcinoma
	Papilloma	Papillary adenocarcinoma
	Cystadenoma	Cystadenocarcinoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Melanocytes	Nevus	Melanoma

Anaplasia – cells resembling stem cells (poorly differentiated)

- Well differentiated – closely resembles tissue of origin
- Well differentiated tumours are usually benign

Anaplasia – cell do NOT de-differentiate (misnomer) – almost always indicates malignancy

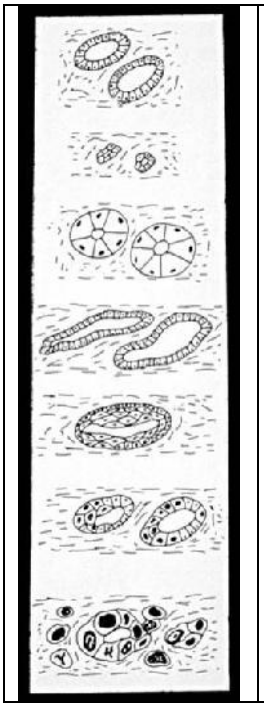
- Pleomorphism
- Hyperchromatic, large nuclei
- Bizarre nuclear shapes, distinct nucleoli
- Lots of mitosis, atypical mitosis
- Architectural anarchy

Dysplasia – disorderly growth

- Pleomorphic, hyperchromatic, large nuclei, lots of mitosis, architectural anarchy
    - Different in that it does NOT have bizarre nuclear shapes/distinct nucleoli
- Describe disorderly changes in non-neoplastic epithelial cells
- Graded as mild, moderate, severe
    - Mild and moderate are reversible
    - Severe usually progresses to carcinoma in situ (CIS)
        Next step is an invasive carcinoma

- Differentiation – only neoplastic (abnormal differentiation of) cells, can apply to any cell type
- Dysplasia – only non-neoplastic cells, on applies to epithelial cells

- Non-neoplastic epithelial cells
    - Mild dysplasia moderate dysplasia severe dysplasia carcinoma in situ
- Neoplastic cells
    - Well differentiated moderately differentiated poorly differentiated anaplastic



Normal

Atrophic

Hypertrophic

Hyperplasia

Metaplasia

Dysplasia

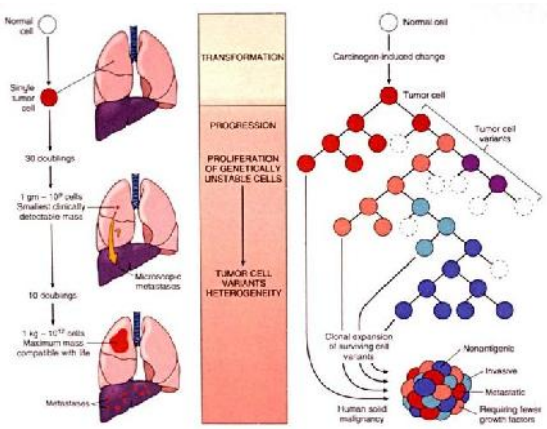
Invasive carcinoma

Malignant tumors (poorly differentiated) grow faster than benign (well differentiated) ones. Growth is dependent on:

- Blood supply
- Hormonal factors
- Emergence of aggressive sub-clones

Growth fraction = cells that are actively dividing

- Early (subclinical) – high GF
- Later (clinical) – low GF



Type of tumour

- Leukemia, lymphoma, small cell lung cancer – high GF
- Breast, colon cancer – low GF

Treatment

- High GF tumor – chemotherapy/radiation
- Low GF tumor – treat by debulking

Most tumours require at least 30 doublings (1million cells) to be detectable. They have usually already learned to metastasize by then.

Malignant tumours – infiltrate, invade, destroy surrounding tissues. Metastasize to other sites. Not encapsulated

- Carcinoma in situ – malignant tumour not yet broke out of its localized area
    - Invasive carcinoma – started to branch out of its localized area
    - Metastasizing carcinoma – colonized other areas

Metastasis – development of secondary tumor implants in distant tissue

- Dependent on
    - Type of tumor
    - Size of tumor
    - Degree of differentiation of tumour
- Half of all diagnoses with malignancies have metastases at time of diagnosis

3 ways of metastasis

- Seeding
    - Tumor invades body cavity
    - Bits break off at implant on peritoneal cavity
    - Ovarian cancer
- Lymphatic drainage
    - Tumor spreads to local lymph nodes
        - Sentinel lymph node (first node to receive lymph drainage) first
    - Moves through thoracic duct
    - Empties into subclavian vein
    - Carcinomas like to spread this way
- Hematogenous spread
    - Veins are easier to invade than arteries
    - Liver and lungs are most common metastatic destinations
    - Some tumors like other sites better
        - Prostate bone
        - Lung cancers adrenals, brain
    - Sarcomas like to spread this way (so do carcinomas)

- 1.4M cases of new cancer last year
- 565K deaths last year
    - 2nd leading cause of death (after heart disease)
- Most common forms
    - Men – prostrate
    - Women – breast
- Deadliest cancer – lung (for both genders)
- Decreased death rates for
    - Cervical cancer – pap smears
    - Colon cancer – earlier detection
    - Breast cancer – earlier detection
    - Lung cancer in men – less smokers
    - Some types of leukemia – new treatments
- Increased death rates for
    - Lung cancer in women – more smokers

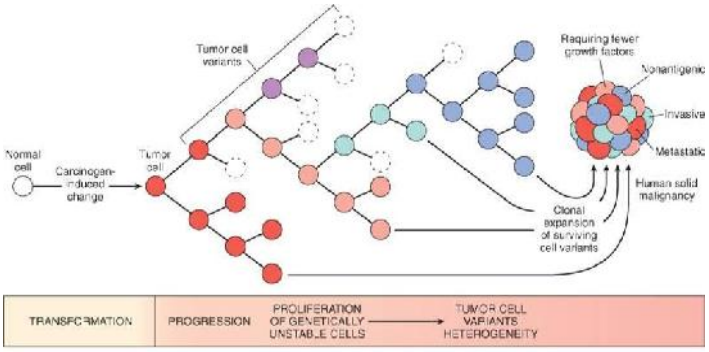
- Environmental factors
    - Breast cancer rate in USA 5x more than Japan
    - Stomach cancer rate in Japan 7x more than USA
    - Liver cancer NOT frequent in USA, frequent in Africa
    - These probably due to environmental (not hereditary) factors
    - Most sporadic cancers caused by environmental factors
        - Sunlight – skin cancer
        - Smoke – lung cancer
        - Alcohol – liver, breast cancers
        - HPV – cervical cancer

Asbestos	roofing, tiles	mesothelioma
Benzene	light oil, solvents	leukemia
Beryllium	missile fuel	lung cancer
Ethylene oxide	ripening agents, fumigants	leukemia
Radon	uranium decay, mines	lung cancer
Vinyl chloride	refrigerants	angiosarcoma and liver cancer
Nickel	welding, ceramics	nose and liver cancers
Cadmium	batteries	prostate cancer

- Age
    - Elderly – most cancers occur between 55-75
    - Children – 10% of all kid deaths, leukemia/lymphoma, CNS tumors, sarcoma
- Heredity
    - Inherited cancer syndromes
        - Dominance
        - Retinoblastoma (Rb)
        - Familial polyposis coli
    - Familial cancers
        - Most common sporadic cancers have familial forms too
        - Breast, colon, ovary, brain
        - Occur earlier, are often deadlier
    - Syndromes of defective DNA repair
        - Recessive
        - Xeroderma pigmentosum
- Acquired preneoplastic syndromes
    - Persistent regenerative cell replication
        - Chronic skin fistula – squamous cell carcinoma
        - Cirrhosis – liver cancer
    - Hyperplastic and dysplastic proliferations
        - Atypical endometrial hyperplasia – endometrial cancer
        - Dysplastic bronchial mucosa – lung cancer
    - Chronic atrophic gastritis – stomach cancer
    - Chronic ulcerative colitis – colon cancer
    - Leukoplakia – squamous cell carcinoma

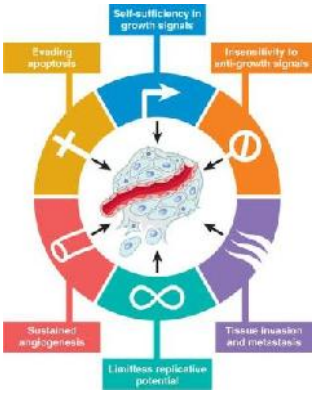
Causes of non-lethal genetic damage (4 genes)

- Proto-oncogenes – genes that promote growth
- Tumor suppressors – genes that inhibit growth
- Genes that regulate apoptosis
- Genes that repair DNA



Cancer progresses in multiple steps

Cancer genes cause bad things in cells

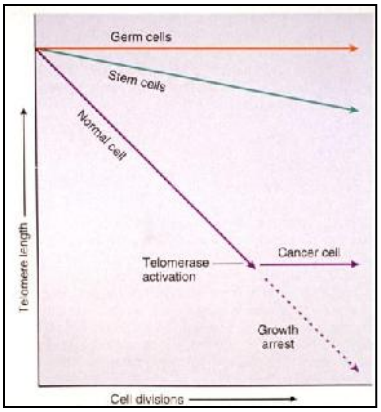


- Autonomous growth, insensitivity to inhibition factors, evasion of apoptosis, limitless replication, sustained angiogenesis, invasion and metastasis

- Proto-oncogene – normal gene whose product promotes cell growth
    - Oncogene – mutated proto-oncogene
    - Oncoprotein – product of an oncogene

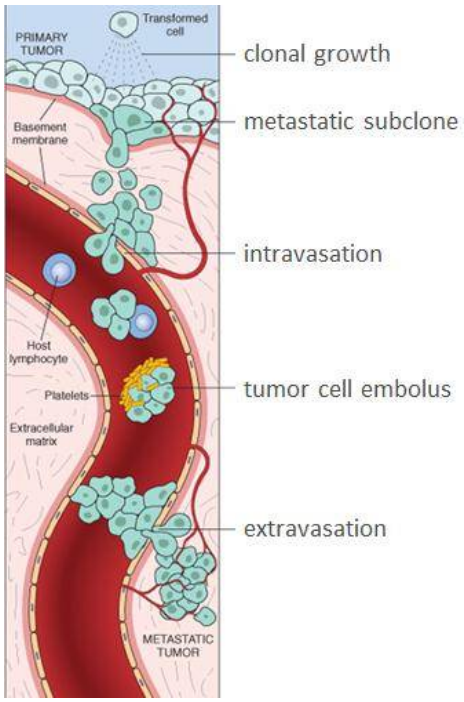
- In normal cells
    - Growth factor binds to receptor
    - Receptor activates signal transducing protein
        Activates 2ndary messenger
    - 2ndary messenger talks to transcription factors
    - Nuclear transcription factors start DNA transcription
    - Cyclins move the cell through the cell cycle
- In cancer cells
    - Growth factors made by cell itself
    - Receptors may be overexpressed or always on
    - Signal transducing proteins may always be on
    - Nuclear transcription factors may always be expressed
    - Cyclins may be overactive
    - All means the cell has uncontrolled division

- RAS – signal transduction gene (always on in cancer) - dominant
- Tumor suppressor genes
    - RB gene – stops cells at G_1 checkpoint
        Mutant Rb is inactive – allows cells to bypass checkpoint
        Patients with 2 mutated genes – increased risk of retinoblastoma, increased risk of other carcinomas
    - P53 gene (genome guardian) – if DNA is damaged, p53 tells Rb to stop cell cycle to allow for repair
        If repair is not possible, p53 tells cell to undergo apoptosis
        Most tumors have p53 mutations
- Evasion of apoptosis – if these proteins are mutated, cell becomes immortal
- Limitless replication – normal cell only replicates 60-70x, telomeres get shorter
    - Stem cells use telomerase to maintain telomere length and keep replicating



- Sustained angiogenesis
    - Tumor cells, like all other cells, need blood supply
    - Can't grow more than 1-2cm away from supply vessels
    - Tumor cells eventually learn how to stimulate angiogenesis
    - Lots of cytokines are involves (VEGF)
    - Tumor vessels are abnormal
        - Normal networks – stable, structure and function of wall and network appropriate to location
        - Tumor networks – evolving, unstable, abnormal function inappropriate to location

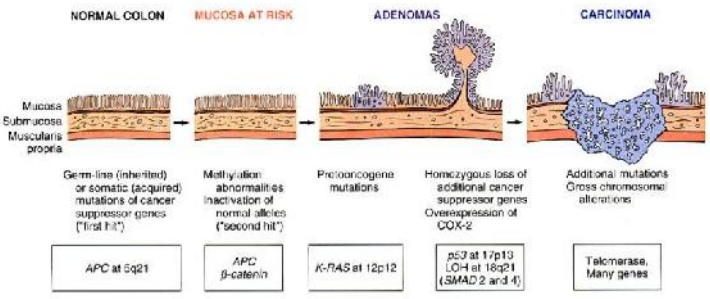
- Invasion and metastasis
    - To invade, tumor cells must
        - Loosen contact between cells
        - Degrade ECM
        - Migrate away from original site (metastasize)
    - Some tumors lodge in nearest capillary bed
    - Some tumors show tropism (preferential site of invasion)



- How genetic mutations arise
    - Constant exposure to mutagenic agents, but corrected because cells are constantly under repair. Inherited defects to those controls increases chance of tumor
        - Cell divisions per day = 10^{11}
        - Spontaneous mutation rate = 10^{-6}
        - Mutations per day = 10^{5}
- Hereditary DNA repair defects
    - Hereditary nonpolyposis colon cancer syndrome
        - Failure of mismatch repair (no spellchecker)
        - Inherited one mutation, acquire the other
        - Familial colon cancers
    - Xeroderma pigmentosum
        - Failure of nucleotide excision repair system
        - Small sun exposure leads to skin cancer

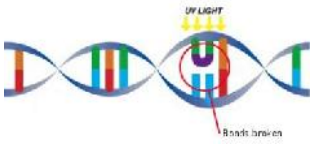
- Steps to cancer
    - Every tumor results from accumulation of lots of mutations (average = 90)
    - Normally, body fixes or rids mutated cells (Rb, p53, etc)
    - For a tumor cell to propagate, mutation must be in one of these guardian/proofing genes

- Chromosomes
    - Genetic damage can be subtle (invisible on karyotype)
    - Or large, visible on karyotype
    - Some karyotype abnormalities occur predictably in certain tumors
        - Leukemias, lymphomas, solid tumors



- Balanced translocations
    - Common!
    - Either place proto-oncogene next to a promoter
    - Or create a fusion gene that makes a bad growth promoting product
    - Most common in hematopoetic tumors (ex:// Ph chromosome)
- Deletions
    - Deletion of part or all of a chromosome
    - Usually deletion of a tumor suppressor gene
    - Most common in solid tumors (ex:// deletion of 13q14 in Rb)

- Agents
    - Chemical
        - Direct-acting agents
            - Carcinogenic as-is
            - Most are chemotherapy drugs
            - Cause secondary malignancies (ex:// leukemia)
        - Indirect acting agents
            - Require conversion to become carcinogenic
                - Hydrocarbons (in tobacco, charred meat)
                - Aflatoxin B (from aspergillus infected grains, nuts)
                - Nitrites (food preservative)
        - Mechanisms
            - Highly reactive electrophile groups bind to DNA
            - Important targets = RAS and p53
    - Radiation
        - Ionizing radiation – causes chromosome breakage, translocations
            - Unprotected miners (lung cancer)
            - Atomic bomb survivors (leukemia, other cancers)
            - Therapeutic head/neck radiation (thyroid cancer)
        - UV light – causes formation of pyrimidine dimers
            - Repair pathways usually fix – but can become overwhelmed
            - Ex:// squamous cell carcinoma, melanoma



    - Bugs
        - HTLV-1 – T-cell lymphoma
        - HPV – cervical cancer
        - EBV – various lymphomas
        - HBV and HCV – hepatocellularcarcinoma
        - H. pylori – gastric cancer, lymphoma

Grading and staging (used for malignant tumors, useful for determining treatment and prognosis)

- Grading (somewhat useful)
  - Tells you how nasty tumor looks
  - Pathologic evaluation of tumor (use microscope)
  - Mitosis, pleomorphism, necrosis, other variables
- Staging (very useful)
  - Tells you how far tumor has spread
  - Clinical evaluations of patient (imaging, surgery)
  - TNM system

Grading system for breast cancer

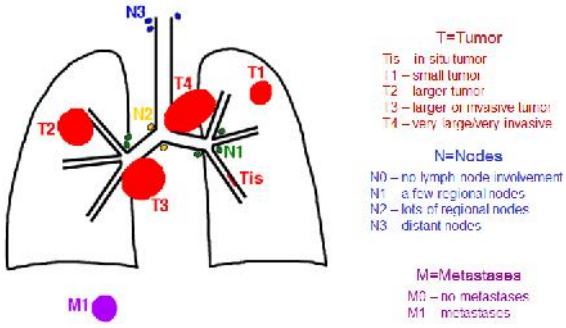
Tubules		Pleomorphism		Mitoses	
lots of tubules	1	small, uniform cells	1	0-9 mitoses/10 hpf	1
some tubules	2	larger, less uniform cells	2	10-19 mitoses/10 hpf	2
rare tubules	3	markedly pleomorphic cells	3	≥20 mitoses/10 hpf	3

add all points together

Grade	Score	5y survival
Low grade	3-5	>95%
Intermediate grade	6-7	80%
High grade	8-9	60%

- Grading – microscopic
- Staging – clinical
- Staging is more useful

TNM staging system for non-small cell lung cancer



TNM staging system for non-small cell lung cancer

Overall stage	T	N	M	Treatment	5y prognosis
Stage 0	Tis	N0	M0	Surgery only	75%
Stage I	T1 or T2	N0	M0	Surgery ± radiation	50%
Stage II	T1	N1	M0	Surgery and radiation ± chemotherapy	30%
	T2	N1	M0		
	T3	N0	M0		
Stage III	T1 or T2	N2	M0	Chemotherapy ± radiation to debulk Maybe surgery	10%
	T3	N1 or N2	M0		
	Any T	N3	M0		
	T4	Any N	M0		
Stage IV	Any T	Any N	M1	Palliative care Maybe chemo or radiation	<2%

- Normal Blood Vessels

Large (elastic) arteries	Aorta, common carotid, iliac	Lots of elastic fibers, pulsatile flow
Medium (muscular) arteries	Coronary, renal	Mostly smooth muscle
Small arteries/arterioles	All smooth muscle	BP control is here
Capillaries	Diameter of RBC	Slow flow, exchange
Venules/veins	Large diameter, thin walls	Compressible, tumor penetrable
Lymphatics	Drain excess ISF	Pass through nodes (infection check) Return bugs (and tumours) to circulation

- Atherosclerosis – atheromas, half of deaths in USA, MI and strokes
    - Non-modifiable – increased age, gender, family history, genetic
    - Modifiable – hyperlipidemia, hypertension, smoking, diabetes, C-reactive protein
    - Lesser risk factors – obesity, physical inactivity, stress, estrogen deficiency, high carb intake, lipoprotein A, trans-fat intake, chlamydia infection
    - Formation process
        - Chronic endothelial injury
        - Monocyte emigration/adhesion
        - Macrophage activation and smooth muscle recruitment
        - Both engulf lipid
        - Smooth muscle proliferation, collagen and ECM lipid deposition
    - Contents = fibrous cap, necrotic center
    - End results – aneurysm and rupture, occlusion by thrombus, critical stenosis
- Prevention
    - Primary (behavioural) – lessen risk factors, statins
    - Secondary (intervention) – aspirin, statins, beta blockers, surgery

- Hypertension – BP>140/90, 25% of population, asymptomatic until late
    - Benign hypertension
        - "Essential hypertension" – idiopathic, mechanism is unknown
            - Reduced renal sodium excretion
            - Vascular changes
            - Genetic and environmental
        - Accelerates atherogenesis
        - Potentiates aortic dissection/stroke
        - Small blood vessel disease = hyaline and hyperplastic arteriosclerosis
        - Secondary hypertension
    - Malignant hypertension

- Aneurysms – localized abnormal vessel dilation
    - "True" = involves all 3 vessel layers
    - "False" = hole covered by hematoma, held in place by extravascular CT
    - Causes = atherosclerosis, cystic medial degeneration of wall, trauma, genetic defects, infection
    - o Abnormal aortic aneurysm
        - Male > 50, atherosclerosis, Marfan's syndrome
        - Below renal arteries, above bifurcation
        - May present as pulsating abdominal mass, can rupture/obstruct branches/embolize
    - o Aortic dissection – blood tracks up through media, creating channel
        - Male 40-60, hypertensive
        - Sudden onset, excruciating pain
        - Can rupture, cause massive hemorrhage or cardiac tamponade
        - Rapid diagnosis and surgery = 60-75% survival

- Vasculitis – inflammation of vessel walls
    - o Many possible symptoms, constitutional signs/symptoms
    - o Immune mediated or infectious

Vessel	Disease	
Large	Giant-cell arteritis	>50, arteries of the head Most common vasculitis Vague (fever), localized (vision loss, headache) Corticosteroids
	Takayasu's arteritis	F, <40, pulseless disease Severe narrowing of aortic branches to upper limbs, ocular disturbances
Medium	Polyarteritis nodosa	Young adults, widespread Varied symptoms, necrotizing in many organs, different stages coexist in same region Fatal if untreated Steroids and cyclophosphamide
	Kawasaki's disease	<4, coronary disease, lymph nodes, strawberry tongue Self-limiting, delayed hypersensitivity reaction Intravenous Ig
Small	Wegender granulomatitis	Mid 40s, Lung, kidney, c-ANCA (Triad symptoms – lungs, kidney, vasculitis) Cavitating lung lesions, palatal ulceration T-cell mediated hypersensitivity Fatal in 1 year if untreated
	Churcg-strauss syndrome	Lung, eosinophils, asthma, p-ANCA Same as Wegender No renal disease Asthma and allergy association
	Microscopic polyangiitis	Lung, kidney, p-ANCA Widespread necrosis of small vessels Antibody response to bugs/drugs, Neutrophils in vessels Type III hypersensitivity Removing offending agent

- Tumors

Hemangioma	Very common benign tumor of blood vessels	Capillary – skin, oral mucosa, sometimes organs - "strawberry" at birth, regresses with time Cavernous – organs, sometimes skin - Cosmetic problem (unless in brain) Pyogenic – rapidly growing red nodules on skin, oral mucosa - Microscopically resembles granulation tissue
Glomus	Benign Very painful	Arise from glomus body cells Distal digits, especially under fingernails Excision is curative
Kaposi sarcoma	Low-grade epithelial malignancy	Clinical course varies (chronic is best) - Chronic – older Ashkenazi Jews - African - Transplant associated - AIDS associated Excision is curative
angiosarcoma	Endothelial malignancy	Skin, soft tissue, breast, liver Risk increase with Arsenic and PVC Well differentiated to anaplastic Rapid metastasis, 5yr survival = 30%

- Heart Failure – endpoint of many heart diseases
    - Very common, most common cases are bilateral
    - Most due to systolic dysfunction
    - Some due to diastolic dysfunction, valve failure, or abnormal load
    - Cardiac response = hormonal release (norepinephrine), frank-starling mechanism, hypertrophy
        - Initially, this works
        - Over time, myocytes degenerate, hearts need more oxygen, myocardium ischemic risk
    - o Left heart failure
        - Blood backs up into lungs = cyanosis, pulmonary edema
            - Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fine rales at lung base
            - Mitral regurge, systolic murmur, irregular irregular heartbeat
        - Ischemic heart disease, systemic hypertension, mitral/aortic valve defect, primary heart disease
        - LV hypertrophy, dilation, LA enlargement (atrial fibrillation)
    - o Right heart failure
        - Blood backs up in body = hepatomegaly, ascites, peripheral edema, splenomegaly
            - Nutmeg liver, enlarged spleen
        - Left heart failure, lung disease, congenital heart disease
        - RV hypertrophy, dilation, RA enlargement

- Congenital heart disease – abnormalities present at birth
    - Faulty embryogenesis – 3rd-8th week
    - Broad spectrum variety, cause unknown in 90% of cases
    - o Left right shunts
        - Atrial septal defect – initially left right shunt (asymptomatic)
            - Eisenmenger syndrome – pulmonary hypertension leads to right left shunt
            - Surgical repair to prevent permanent change and heart failure

Ventricular septal defect – most common congenital heart defect
Most close spontaneously in childhood
Small VSD = asymptomatic
Large VSD = may become right left shunt
Patent ductus arteriosus – allows flow from PA to aorta
Closes spontaneously first 1-2 days of life
Small PDA – asymptomatic
Large PDA – may become right left shunt

- Right left shunts
  Tetraology of fallot – most common cause of cyanotic congenital heart disease
  Caused from VSD allowing RV blood flow into aorta
  4 features – VSD, RV outflow obstruction, override aorta, RV hypertrophy
  Cyanosis, clubbing, paradoxical emboli, erythrocytosis
  Transposition of great arteries – aorta arises from RV instead of LV, pulmonary artery arises from LV instead of RV
  Separation of systemic and pulmonary circulation
  Fatal unless there is a very large VSD
- Obstructions – aortic coarctation (narrowing)
  2 forms:
  Infantile (preductal)
  Adult (productal)
  Cyanosis and low BP in extremities
  Severity is coarctation dependent

- Ischemic heart disease = myocardial perfusion cannot meet demand (lack of O_2)
  Usually from decreased coronary flow
  - Angina pectoris – intermittent chest pain from transient, reversible ischemia
    Typical (stable) – pain on exertion, fixed narrowing of coronary artery
    Prinzmetal (variant) – pain at rest, coronary artery spasm of unknown etiology
    Unstable (pre-infarct) – increase pain with no exertion, plaque disruption and thrombosis
  - Acute MI – necrosis of heart tissue caused by ischemia
    1.5M/year, most via acute coronary artery thrombosis
    Sudden plaque disruption, platelet adherent, coagulation cascade, thrombus occluding lumen, irreversible injury/death in 20-40min
    Prompt reperfusion can salvage myocardium
    Clinical features = severe chest pain w/ or w/o radiation not relieved by nitro or rest, sweating, nausea, dyspnea
    Lab tests – troponin increase within 2-4h, remain elevated for a week
    CKMB increase within 2-4h, return normal in 72h
    Complications – contractile dysfunction, arrhythmias, rupture, chronic progressive heart failure
    Prognosis – remaining function and perfusion dependent
    Overall 1 year mortality = 30%, 3-4% mortality per year after
  - Chronic IHD
  - Sudden cardiac death

- Hypertensive Heart Disease – can affect either ventricle
    - Cor Pulmonale – RV enlargement from pulmonary hypertension via primary lung disorder
        - Myocyte hypertrophy
    - Reasons for heart failure in hypertension is poorly understood

- Valvular heart disease – stenosis and/or insufficiency
        - Stenosis = failure to open
        - Insufficiency = failure to close
        - Murmurs, outcome dependent on severity and speed of development
    - Calcific aortic stenosis – part of aging process
        - Normal or congenitally bicuspid valves
        - Results in increased LV pressure, LV hypertrophy, relative ischemia
        - Angina, CHF, fainting
    - Mitral valve prolapse – ballooning of mitral valve
        - Common – 5% of USA, F>M
        - Myxoid/mucoid change within leaflet
        - Usually asymptomatic, pathogenesis unknown
    - Rheumatic valvular disease – rheumatic fever – systemic inflammation a few weeks after strep throat
        - Valve scarring causing stenosis and regurgitation
            - Ab against strep cross-reacts with heart and joint Ag
            - 2-3wks after infection, patient gets migratory polyarthritis and pericardial friction rub and arrhythmias
        - Chronic disease can reappear decades later, long term prognosis variable
            - Mitral stenosis, LA enlargement, thrombi, increased risk of infective endocarditis
    - Infective endocarditis – microbial invasion of heart valves, endocardium
        - Acute – highly virulent bug attacks normal valve, half of patients dead within days/weeks
        - Subacute – low virulence bug colonizes normal valve, slow onset, long course, most patients recover
        - Symptoms = fever, flu-like symptoms
        - Complications = septicemia, arrhythmias, renal failure, systemic emboli, vegetations on heart valves, splinter hemorrhage of nail bed

- Cardiomyopathies – diverse group of disorders, intrinsic myocardial dysfunction
        - Lots of causes, many idiopathic
    - Dilated cardiomyopathy – heart dilates/enlarges, can't contract well
        - Causes – virus, toxin (^OH), genetics, peripartum
        - Slow progressing CHF, 70% dead in 5 years
    - Hypertrophic cardiomyopathy – massively hypertrophied LV can't fill
        - Cause – mutation in sarcomere protein gene
        - Atrial fibrillation, CHF, arrhythmia, sudden death
        - Treat via drugs to promote ventricular relaxation, surgically excise part of septum
        - 4% of patients die per year
    - Restrictive cardiomyopathy – stiff heart wall, cannot fill during diastole
        - Idiopathic of secondary to systemic disease (amyloidosis, hemochromatosis, sarcoidosis)
        - Shortness of breath, pheripheral edema
        - Treatment not helpful, 70% of patients dead in 5 years

- Pericardial disease
    - Pericarditis – atypical chest pain
        - Primary (infectious) or secondary (MI, radiation, pneumonia)
        - Dangers – tamponade, chronic fibrosis
    - Pericardial effusion
        - Serous (CHF), seroanguinous (aortic dissection), chylous (lymph obstruction)
        - Outcome dependent on pericardial sac stretchiness
        - Slow = asymptomatic
        - Sudden = catastrophic

- Cardiac Tumors
    - Metastatic – most common
        - Heart is a rare site for metastases
        - Most common = lungs and lymphoma
    - Primary tumors – uncommon
        - Most are benign
        - Most common = myxoma

- Population >65y/o
    - 60% healthy
    - 35% chronically ill – arthritis, hypertension, etc
    - 5% frail – something non-medical combined with chronic illness causing disability
- Causes of mortality – heart disease, cancer, stroke, COPD, pneumonia, flu
- Causes of morbidity – arthritis, hearing/vision loss, diabetes, alzheimer's, osteoporosis, constipation
- ADL – activities of daily living = cooking, clothing, showering, defecating, etc
- IADLS – instrumental activities of daily living (doesn't have to be done daily, but MUST be done periodically) = laundry, cleaning, etc
- 5 functional domains = medical, familial/social, financial, environmental, cognitive/emotional
    - Physical health, psychological health, social heath, financial health, environmental health
- Balancing act – disease risk factors / disease end points --------- treatment risk factors / treatment side effects
- Coronary Arterial Disease - #1 cause of death in old people
- Heart failure – inability to pump enough blood
    - Systolic failure – decreased ejection fraction
    - Diastolic failure – relaxation failure, not enough blood filling time
- Dyslipidemia – high LDL, low HDL, high TG
    - Asymptomatic, risk factor for 2ndary prevention
- Arrhythmias – atrial fibrillation
    - Asymptomatic, risk factor for stroke, rapid ventricular response = problem
        - Treat via rate control, anticoagulants
    - Bradycardia – passing out (pacemaker)
- Valvular disease
    - Aortic stenosis, mitral valve prolapse, mitral regurgitation

- Drugs
    - Diuretics – thiazide and loop
        - HCTZ, furosemide, Lasix
        - Takes off fluid, but can cause electrolyte imbalance/dehydration (decreased Na^{+})
    - Beta-blockers – "olol"s
        - Metroprolol, atenolol
        - Slows heart rate (atrial fibrillation, hypertension), can cause lethargy, exacerbate bronchospasm
    - Ca^{++} blockers – diltiazem, verapamil, amlodipine, nifedipine
        - Decrease BP, slow heart rate (first 2 drugs)
            - Some speed up heart rate
        - Ankle and feet edema, bradycardia, tachycardia
    - ACE inhibitors – "opril"s
        - Enalapril, lisinopril
        - Beta-blockers and ACE inhibitors reduce recurrent heart attacks
        - Affects renin-angiotensin pathway, can cause dry cough, hyperkalemia in kidney
    - Angiotensin receptor blockers – "artan"s
        - Losartan, valsartan
        - Similar to ACE inhibitors
    - Alpha blockers – "azosin"s
        - Doxazosin, terazosin
        - Affects alpha-adrenergic system, can cause orthostatic hypertension
            - Treat men with enlarged prostate
    - Nitrates – "isosorbide _____"
        - Numerous types, relaxes smooth muscle (dilates coronary artery), can cause headaches
    - Platelet inhibitors
        - Aspirin, thienopyradine
        - Prevent platelet aggregation, have long half-lives
    - Anticoagulants
        - Heparin, factor Xa inhibitor, warfarin

Medication	Coronary arterial disease	hypertension	Heart failure	Rhythm/valve
Diuretic		++	++	+
Beta-blocker	++	++	++	++
Ca^{++} blocker	+	++	++	++
ACE inhib./ARB	++	++	++	+
Alpha blocker		+		
Nitrates	++			+
Anti-platelets	++	+	+	+
anticoagulants	+		+	++

Esophagus

- Hiatal hernia – dilated portion of stomach protrudes above diaphragm
    - Common, usually asymptomatic
    - Heartburn, reflux, ulceration, bleeding
    - Sliding – region by cardiac sphincter protrudes
    - Rolling – region not by cardiac sphincter protrudes
- Mallory-weiss syndrome – grastric/esophageal junction tears
    - Severe vomiting (chronic alcoholics)
    - Bleeding, pain, infections
    - Treat with balloon tamponade, cauterize arteries, epinephrine
    - Prognosis – usually heals, sometimes fatal
- Barrett Esophagus – metastatic replacement of squamous with columnar epithelium
    - Can lead to risk of dysplasia leading to carcinoma
        30-100x risk of adenocarcinoma
    - Complication of long standing esophageal reflux
    - Endoscopic screen for high-grade dysplasia
- Esophageal carcinoma

Adenocarcinoma	Squamous cell carcinoma
- Most common in USA - Risk factor – barrett esophagous - Distal 1/3 of esophagus - Insidious onset, late obstruction	- Common global - Risk factors – esophagitis, smoking, ^OH, genetics - Middle 1/3 of esophagus - Insidious onset, late obstruction

Stomach

- Gastritis – chronic mucosal inflammation
    - Asymptomatic or discomfort
    - Cause – helicobacter pylori, autoimmune gastritis
    - Danger – intestinal metaplasia
- Helicobacter pylori asymptomatic gastritis :
    - Symptomatic gastritis, ulcer, carcinoma, lymphoma
    - Gastritis – acute mucosal inflammation (transitory)
        Causes – NSAIDs, ^OH, smoking
        Superficial or full-thickness, can lead to erosions
        Asymptomatic or pain, vomit, hematemesis
    - Ulcer – erosion of mucosa into submucosa
        Causes – NSAIDs, H. pylori
        Symptoms – epigastric pain
        Danger – bleeding, perfusion
        Neutrophils release cytokines that do cellular damage (immunopathogenesis)
    - Gastric carcinoma (both asymptomatic)
        Intestinal type – intestinal metaplasia (glandular morphology)
            Risk factors – chronic gastritis, bad diet
        Diffuse type – gastric glands (signet ring morphology)
            Risk factors – undefined

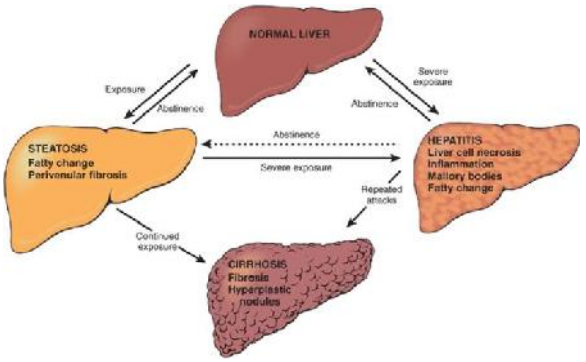
Intestinal

- Diverticulosis
  - Herniation through muscle wall of mucosa/submucosa
  - Older patients with low fiber intake
  - Sigmoid colon
  - Asymptomatic unless infected (diverticulitis)
- Inflammatory Bowel Disease
  - Crohn disease – anywhere, patchy, transmural
    Poor response to surgery, increased risk of cancer
  - Ulcerative colitis – colon only, continuous, superficial
    Good response to surgery, increased risk of cancer
- Adenoma – benign gland, may become dysplastic
  - Common, 50% of people >60y/o
  - Dangerous when >1cm, villous architecture, severely dysplastic
- Colon carcinoma – almost always arise in adenomatous polyp
  - Low fiber, high fat, high refined carb intake
  - Silent for years, fatigue, weakness, iron deficiency anemia, occult bleeding, crampy pain
  - 4% stage 4, 90% stage 1 prognosis at 5 years

Hepatic

- Viral hepatitis
  Acute – jaundice
  Chronic – cirrhosis
  Fulminant – liver failure
  - Hep B – from acute infection to…
    60-65% subclinical phase – all recover
    20-25% acute phase – 99% recover, 1% fulminant (death)
    5-10% become carriers
    4% chronic – 20-30% progress to cirrhosis, to cancer or death
    The rest – some recover, others get cancer and die
  - Hep C – from acute infection to…
    15% resolution
    1% fulminant (death)
    85% chronic – 80% become stable, 20% get cirrhosis (50% stable, 50% cancerous = death)
- Jaundice elevated bilirubin
  - Conjugated hyperbilirubinemia
    Decreased liver excretion (hepatitis)
    Decreased bile flow (tumor blocking bile duct)
  - Unconjugated hyperbilirubinemia
    Increased production (hemolytic anemia)
    Decreased uptake (hepatitis)
- Liver Function Tests
  - Hepatocyte integrity – AST, ALT
  - Biliary function – serum bilirubin, serum alkaline phosphatase
  - Hepatocyte function – serum albumin, Prothrombin time

- Cirrhosis – permanent fibrotic, nodular liver
    - ^OH, hepatitis
    - Leads to portal hypertension, liver failure, increased risk of liver carcinoma
    - Portal hypertension – decreased blood flow through liver
        - Largest cause = cirrhosis
        - Symptoms = ascites, venous shunts, congestive splenomegaly, hepatic encephalopathy, periumbilical caput medusae
- Liver failure – endpoint of severe liver disease
    - Fulminant hepatitis, cirrhosis, drug overdose
    - Jaundice, edema, bleeding, hyperammonemia
    - Multiple organ system failure – hepatic encephalopathy, hepatorenal syndrome
    - Oral manifestations = hematomas, gingival bleeding, jaundiced mucosa, glossitis (^OH), reduced healing
- Alcoholic liver disease – 100K-200K deaths/year
    - Steatosis, hepatitis, cirrhosis, Mallory bodies
    - Short term ingestion – 8beers/day – reversible steatosis
    - Long term ingestion – 5beers/day – irreversible steatosis
    - Abstinence for 5 years = 90% recovery
    - Continued drinking for 5 years = 50-60% recovery
    - Causes of death in end-stage liver disease
        - Liver failure, massive GI bleed, infection, hepatorenal syndrome, hepatocellular carcinoma, Mallory bodies



- Hereditary hemochromatosis – autosomal recessive, increased body iron
    - Mutations in hematochromatosis gene (regulates iron absorption)
    - Cirrhosis, skin bronzing, liver carcinoma
    - Early detection and treatment (iron chelation) = normal life expectancy
- Wilson disease – autosomal recessive, increased body copper
    - Mutation in gene regulating copper excretion
    - Acute and chronic liver disease, neuropsychiatric manifestations, Kayser-Fleisher rings in cornea
    - Treat via copper chelation
- Hepatocellular carcinoma – rapid increase in liver size, ascites, fever, pain
    - Strongly associated with Hep B and C, chronic liver disease, and aflatoxins (peanut and grain mold)
    - Drastic increased alpha-fetoprotein level
    - Median survival = 7months – death via bleeding, liver failure, cachexia
- Metastatic carcinoma – most common malignancy in liver
    - Usually multiple lesions, most common primaries = colon, lung, breast, pancreas, stomach

Gall Bladder

- Cholelithiasis – common (10% of adults in USA)
    - Cholesterol stones (female, fat, fertile, forty)
    - Pigment stones (bilirubin) – Asian, hemolytic anemia, biliary infections
    - Asymptomatic OR excruciating pain radiating right upper quadrant to right shoulder
    - Complications – holecystitis, empyema, perforation, fistula, obstruction, pancreatitis
- Cholecystitis

Pancreas

- Normal pancreas
    - Exocrine – makes digestive enzymes
        - Disease – pancreatitis, cystic fibrosis, tumors
    - Endocrine – makes insulin, glucagon, other hormones
        - Disease – diabetes, tumors
- Acute pancreatitis – inflammation, reversible destruction of pancreas
    - Cause – ^OH, gallstones
    - Symptoms – abdominal pain radiating to back
    - Test – elevated serum amylase, lipase
    - Prognosis – recovery, 5% die in first week
- Chronic pancreatitis – longstanding, irreversible destruction of pancreas
    - Cause – ^OH, idiopathic
    - Symptoms – silent, bouts of jaundice and pain
    - Prognosis – poor, 50% mortality over 20 years
- Pancreatic carcinoma – 4th leading cancer death in USA
    - Cause – smoking
    - Highly invasive
    - Silent until late, then pain and jaundice
    - High mortality – 5% survival after 5 years

Pneumonia

Alveolar – bacterial infections
Bronchopneumonia – bacterial
Lobal – strep. Pneumonia
Interstitial – viral, mycoplasma

- Pathogenesis – aerosol inhalation, aspiration of infected objects, hematogenous spread
- Predisposing factors – decreased cough reflect, ciliary injury, decreased alveolar macrophage, edema/congestion, secretion retention

- Lung abscess
  - Localized suppurative necrosis – frequently mixed infections
    Staph, strep, gram –^{ve}, anaerobes
  - Pathogenesis – aspiration, pneumonia, septic emboli, tumors, direct infection
- Pulmonary TB – mycobacterium TB
  - Inhalation of infected droplets
    Primary – single granuloma inside parenchymal and hilar lymph nodes (Ghon complex)
    Most common – infection does not progress (cough, scanty mucoid sputum later purulent)
    Progressive primary pneumonia – patchy infiltrates, cavitation, hilar lymphadenopathy
    - Healed primary TB – calcified peripheral node, calcified lymph node (Ghon complex)

    Military dissemination – malaise, weight loss, night sweats, fever
    - Lymphadenopathy, back pain, GI/renal disturbance, heart failure, neurologic

    Secondary – infection through reactivation in previously sensitized individual
    Cavitary fibrocaseous lesions
    Bronchopneumonia
    Military dissemination
  - Lab tests and Treatment
    Positive mantoux test does not mean clinically active infection
    Sputum smear positive for acid-fast organisms
    Confirm with culture/molecular testing
    Non-infectious after 3-6 months
  - Dental Management
    New, active TB – only treat emergency, and in hospital isolation
    After 2-3 weeks treatment – treat normal
    History of TB – treat normal
    Positive TB – treat normal
    Clinical signs suggestive of TB – do not treat
  - Oral complications
    Painful deep tongue ulcers - uncommon
    Cervical, submandibular lymphadenitis – scrofula

Chronic Obstructive Pulmonary Disease

- Chronic bronchitis – persistent cough with sputum for at least 3 months over 2 consecutive years
  - Airway inflammation, mucous producing cell hyperplasia, squamous metaplasia, cilia cell injury
  - Caused from smoking
  - Prominent vascular markings in chest X-ray
  - No cure, treat with early management
    - Regular exercise, stop smoking, good nutrition, adequate hydration, oxygen therapy ($SpO2 \leq 88$), drugs
    - Treat in upright chair, use inhalers before appointment, use pulse oximetry, low dose diazepam, supplemental steroids
    - Avoid rubber dam, sedation, narcotics/barbiturates, antihistamines/anticholinergics, macrolides/ciproflaxin
    - Oral manifestations – halitosis, extrinsic tooth stain, nicotine stomatitis, periodontal disease, oral cancer
  - Blue bloaters – fat, cyanotic, edematous, breathless
    - FVC – forced vital capacity – maximum volume inspired/expired
    - FEV1 – forced exhalation volume 1s – normal if >80%
      - >50% – moderate
      - >30% – severe
      - <30% – very severe, <50% with chronic respiratory failure – very severe
    - PEFR – peak flow
    - FEV1/FVC – COPD if <0.7
- Emphysema – pink puffers
  - Overt distention of lungs, flattened diaphragm in X-ray
  - Centracinary – destruction of central portion, distal lobes preserved
    - Upper lobes, caused from smoking
  - Panacinar – uniform injury
    - Lower lobes, caused from alpha-1-antitrypsin deficiency
- Bronchiectasis – dilatation of bronchi and bronchioles secondary to chronic inflammation
  - Associated conditions – obstruction, cystic fibrosis, immotile cilia, necrotizing pneumonia
    - Lung has giant cavitations in it
- Asthma – chronic inflammatory respiratory disease
  - Airway hyper reactivity
    - Extrinsic – atopic, allergenic – food, pollen, dust, etc
    - Intrinsic – non-atopic – initiation by infections, drugs, pollutants, chemical irritants
  - Mild – symptoms <1h, do not occur daily
  - Moderate – daily symptoms affect sleep and activity
  - Severe – ongoing symptoms limit normal activity, require emergency hospitalizations
    - No single test, multiple test combination
  - Treat via corticosteroids, leukotriene inhibitors, beta-adrenergic agonists, anticholinergics
  - Schedule late morning appointments, use rescue inhaler before procedures, pulse oximeter during procedures, stress free environment
  - Avoid precipitating factors, barbiturates/narcotics, aspirin, NSAIDs, antihistamines, macrolide and ciproflaxin
  - Oral manifestations – mouth breathing complications, increased gingivitis/secondary caries secondary to beta-agonist inhaler use, oral candidiasis secondary to steroid inhaler use

Other Pathologies

- Atelectasis – collapse or incomplete lung expansion
    - Resorption – obstruction of airway – secretions (mucus plug), aspiration, tumors
    - Compressive – pleural effusion or pneumothorax – hydrothorax, pneumothorax, hemothorax, exudate in pleural cavity, tumor
- Pulmonary edema
    - Cardiogenic – increased hydrostatic pressure – heart failure, mitral stenosis
    - Non-cardiogenic – decreased oncotic pressure – nephrotic syndrome, liver disease
    - Microvascular injury – break in vessel – infection, aspiration, drugs, radiation
- Diffuse alveolar damage/acute respiratory distress syndrome
    - Injury to pneumocytes and endothelial cells via free radicals, activated neutrophils/macrophages, surfactant loss
    - Viral infections, gas inhalation/liquid aspiration, drugs, chemical, trauma, hypotension, sepsis, radiation
    - Acute (exudative) stage
    - Proliferative/organizing stage
- Pulmonary embolism – usually from leg veins
    - Large emboli (10%) – sudden death
    - Small emboli (70%) – silent, infarct, hemoptysis
    - Medium (20%) – infarct
- Pulmonary hypertension
    - Primary – idiopathic
    - Secondary (most common) – COPD, chronic interstitial pulmonary disorder, chronic heart failure, recurrent pulmonary emboli
- Hypersensitivity pneumonitis – immunologically mediated disorder affecting airways and interstitium
    - Farmer's lung, pidgeon breeders, air conditioner lung
- Usual interstitial pneumonia/idiopathic pulmonary fibrosis
    - Progressive fibrosing disorder of unknown cause
    - 30-50y/o
    - Cur pulmonale (respiratory failure) in 5 years
- Pneumoconioses – disorders from inhalation of foreign objects, mainly metals
    - Coal worker's pneumoconiosis
    - Silicosis
    - Asbestos

Lung Carcinoma

- Primary cause of cancer deaths in USA
- 85-90% from smoking, 1% from asbestos, rarely arsenic, chromium, mustard gas, nickel, vinyl chloride, bis ether
    - 0.3-3.0% passive smoking, 3-14% radon
- Potentially curable
    - Asymptomatic, cough, hemoptysis
- Incurable
    - Dyspnea, chest pain, anorexia/weight loss, hoarseness, bone pain
- Adenocarcinoma – 3x risk in smokers
    - Peripheral invasion, 15-20% survival/5 years
    - Most common global
- Adenocarcinoma bronchiolalveolar type – increased risk in smokers
    - Single or multiple tumor nodes (miliary tumor)
    - Pneumonic form (miliary tumor)
    - NONINVASIVE tumors which line alveolar surface
    - Pneumonic presentation – poor prognosis

- Squamous cell carcinoma – 25x risk in smokers
    - Second most common type
    - Bronchial squamous cell metaplasia
    - Centrally located, may cavitate (2/3 central, 1/3 peripheral)
    - Keratinization, intercellular bridging
- Large cell carcinoma
    - Gross – peripheral lesion
    - Microscopic – wastebasket group of tumors that don't fit criteria of anything else
    - Prognosis similar to adenocarcinoma
- Small cell carcinoma – 95% of patients smoke
    - Worst prognosis – essentially removes patient from consideration of resection
    - Over 75% of cases present stage III or IV

- Mesothelioma – malignant tumor of mesothelial cells
    - Highly malignant
    - 70% patients exposed to asbestos
    - NOT related to smoking
-

- Azotemia – increased BUN, creatinine
- Uremia – azotemia + other problems
- Acute renal failure – oliguria
- Chronic renal failure – prolonger uremia

Glomerular diseases

Nephrotic Syndrome – leaky glomerulus lets proteins out	Nephritic Syndrome – inflamed glomerulus compromises blood flow and filtration
- Massive proteinuria - Hypoalbuminemia - Edema - Hyperlipidemia/uria	- Hematuria - Oliguria - Azotemia - Hypertension
Adults – systemic disease (diabetes) Children – minimal change disease Characterized by loss of foot processes	Post-infectious GN, IgA nephropathy Immunologically mediated Characterized by proliferative changes and inflammation

- Nephrotic syndrome
    - Minimal change disease
        - #1 cause of nephrotic syndrome in kids
        - Loss of foot processes
        - Unknown pathogenesis
        - Good prognosis
    - Focal segment glomerulosclerosis
        - Primary or secondary
        - Some focal glomeruli show partial/segmental hyalinization
        - Unknown pathogenesis
        - Poor prognosis
    - Membranous neuropathy
        - Autoimmune reaction against unknown renal antigen
        - Immune complexes
        - Thickened GBM
        - Subepithelial deposits/spikes

- Nephritic syndrome
    - Post-infectious glomerulonephritis – sore throat, face bloat, pee coke
        - Children after strep throat
        - Immune complexes
        - Hypercellular glomeruli
        - Subepithelial lumps
    - IgA neuropathy – possibly recurrent/chronic
        - Very common
        - Children with hematuria after URI
        - IgA in mesangium
        - Variable prognosis

Tubular and interstitial diseases

- Inflammatory lesions
    - Pyelonephritis
        - Invasive kidney infection – scarring causing blunted calyx
        - Usually ascends from UTI
            - Women, elderly
            - Patients with catheters or malformations
            - Dysuria, frequency
            - E.coli and proteus (associated with kidney stones) infections
                - E.coli – majority in uncomplicated cases, minority in complicated cases of UTIs
        - Fever, flank pain
        - E.coli and proteus infections
    - Drug-induced interstitial nephritis
        - Antibiotics, NSAIDS
        - IgE and T-cell mediated immune reaction
        - Fever, eosinophilia, hematuria
        - Patient usually recovers, but analgesic nephritis is bad
- Toxic/ischemic lesions
    - Acute tubular necrosis
        - Most common cause of acute renal failure
        - Reversible tubular injury
        - Many causes – ischemic (shock), toxic (drugs)
        - Most patients recover

Blood Vessel Diseases

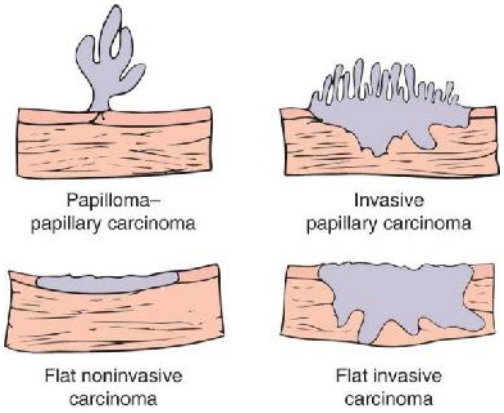
- Benign nephrosclerosis – usually idiopathic
    - Found in patients with benign hypertension
    - Hyaline thickening of arterial walls
    - Leads to mild functional impairment
    - Rarely fatal
- Malignant nephrosclerosis
    - Malignant hypertension
        - 5% of hypertensive cases
        - Super high BP, encephalopathy, heart abnormalities
        - First sign often headache, scotomas
        - Decreased blood flow to kidney leads to increased renin, increasing BP
        - 50% 5y survival
    - Hyperplastic vessels
    - Ischemia of kidney
    - Medical emergency

Cystic Diseases

- Adult polycystic kidney disease
    - Autosomal dominant
    - Huge kidneys full of cysts
    - Asymptomatic until 30s – very common (1/1000) – starts in childhood but not symptomatic until adult
    - Associated with brain aneurysms
- Childhood polycystic kidney disease
    - Autosomal recessive
    - Numerous small cortical cysts
    - Associated with liver cysts
    - Patients often die in infancy

Tumors

- Renal cell carcinoma
    - Derived from tubular epithelium
    - SMOKING, hypertension, cadmium exposure
    - Hematuria, abdominal mass, flank pain
    - 50% survival 5y if metastitc
- Bladder carcinoma
    - Derived from transitional epithelium
    - Presents with painless hematuria
    - Prognosis depends on grade and depth of invasion
    - 50% survival over 5y



Pathology Study Notes:

1: Anemia

Hematopoetic Stem Cells:

- Myeloid:
    - Myeloblast
    - Immature monocyte
    - Megakarocyte
    - Pronmoblast (RBC)
- Lymphoid:
    - Lymphocytes

LAB TESTS:
Complete Blood Count (CBC): looks at RBC, WBC, platlets
RBC: number of cells
Hemoglobin: the amount of hemoglobin you have (Anemia you don't have enough)
Hematocrit: volume of RBC's you have

Complete Blood Count (CBC):

- MCV: Mean Cell Volume = microcytic, normocytic, macrocytic
- MCHC: Mean Cell Hemoglobin Concentration = hypochromic, normochromic (tells you how much hemoglobin each cell is carrying around)

Size variations: Anisocytosis
Shape variations: Poikilocytosis

ANEMIA:

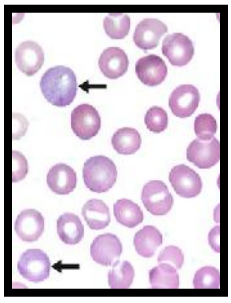
- A reduction below normal in hemoglobin or RBC number
- Symptoms: pale skin and mucous membranes, jaundice, tachycardia, breathlessness, dizziness, fatigue

SPECIFIC TYPES OF ANEMIA: 3 WAYS TO GET ANMEIA =

LOSS OF BLOOD

- Cause may be trauma, acute blood loss. At first the hemoglobin is normal and after 2-3 days you see reticulocytes (young RBC precursors which are bigger than normal). Chronic blood loss is different because it causes iron deficiency anemia.

- Reticulocytes: bigger, younger, have some RNA in them giving them their bluish/purple color instead of the red in normal RBC

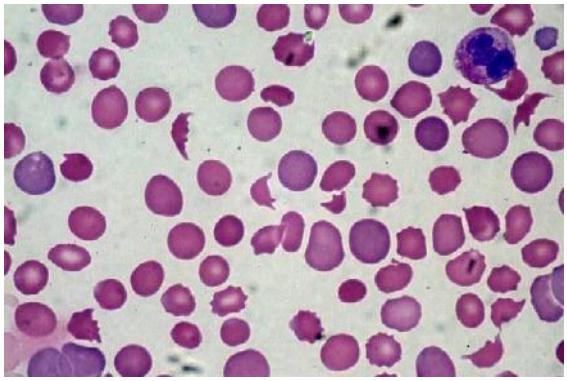


DESTROY TOO MUCH BLOOD (Hemolytic Anemias)

- Chronic vs Acute
- Chronic: inherited, not too bad, can become acute if something happens
- Acute: suddenly, not inherited (ex: antibodies)
- Signs of destruction: increase bilirubin, increase Lactate dehydrogenase enzyme, low haptaglobin (carrier molecule of free hemablobin)

Extracorpuscular reasons

MICROANGIOPATHIC HEMOLYTIC ANEMIA:



RBC's get ripped up in small blood vessels, physical trauma to red cells, SCHISTOCYTES (funny shaped RBC's) and find out why cause some causes are very serious. There is activation of the coagulation cascade causing fibrin strains in small vessels where passing RBC's get snagged as they rush thru and end up looking weird called : Schistocytes (which is a medical emergency, always pathologic, pointy shaped RBC). There is a special kind called Triangulocyte

Causes of MAHA:

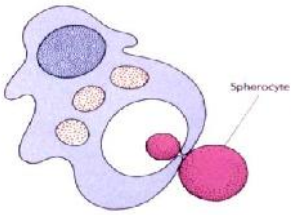
- A MOST
- Artificial heart valve, malignancy, obstetric complications, sepsis, trauma

AUTOIMMUNE HEMOLYTIC ANEMIA:

Temp at which antibody binds: can do DAT (Direct Antiglobulin Test)

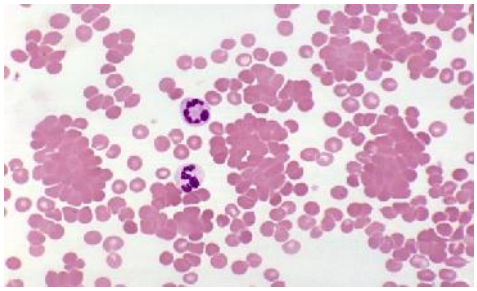
Warm AIHA (WARM GISS)

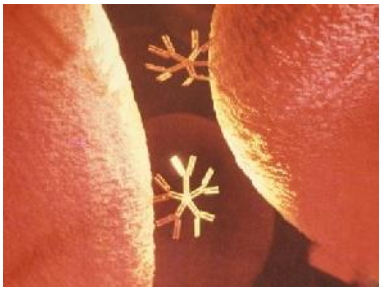
- IgG, Spleen, Spherocytes



Cold AIHA (COLD CIMA)

- IgM, complement, Intravascular hemolysis, Agglutination





Intracorpuscular reasons

SICKLE CELL ANEMIA

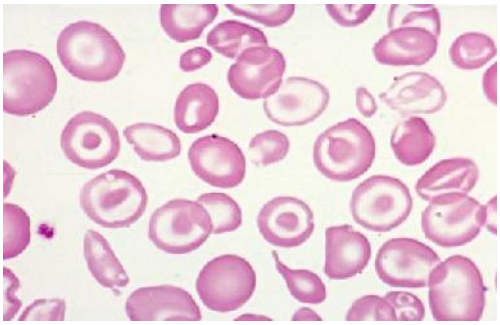
- Hemoglobinopathy (qualitative defect in hemoglobin, point defect in beta chain)
- Single amino acid substitution (point mutation) in beta chain of hemoglobin of valine to glutamate
- Can be heterozygous (sickle trait but no symptoms) or homozygous (double hit and have symptoms)
- Sickle cells are nasty, fragile (burst easily) and get stuck to vessels and clog up vessels, aggregates and polymerizes (sticks together) on deoxygenation
- Lesions on hands/feet common due to blood vessel clogged up (infarct distal to clog)
- In spleen: infarct, heal and form scar, over and over again, no more spleen (spleen gets rid of encapsulated bugs)

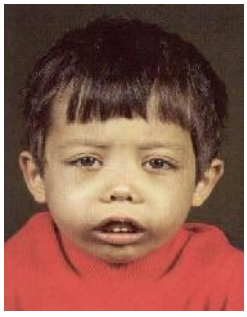
Clinical Findings:

- Blacks, 8% heterozygous
- Severity variable
- Chronic hemolysis, vaso-occlusive disease, and increase infections (autosplenectomy)
- Treatments: prevent triggers, vaccinate, transfuse (wt normal blood)

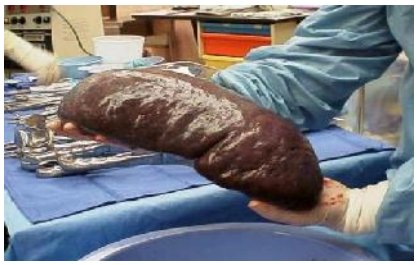
THALASSEMIA

- Quantitative defect in hemoglobin,
- Cant make enough alpha and beta chains
- Variable disease severity
- Hypochromic (low hemoglobin), microcytic (small in size) anemia with increased RBC and TARGET cells
- Alpha more serious cause beta can get help from delta
- Medullary expansion





HEREDITARY SPHEROCYTOSIS

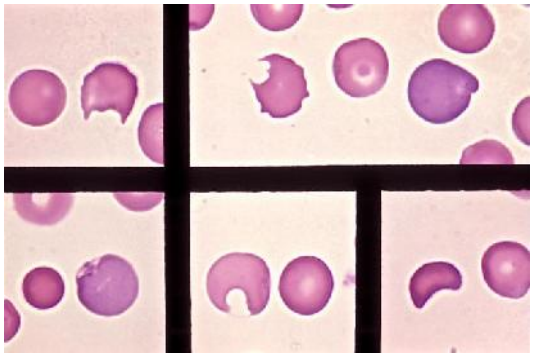
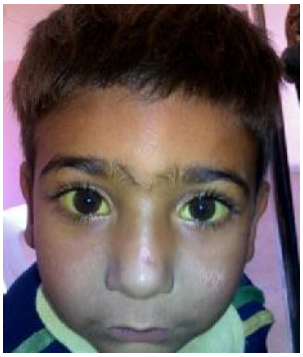


- Problem with RBC membrane
- Lots of spherocytes
- Spectrin defect (proteins that attack cytoskeleton to the membrane)
- Splenectomy is curative (symptoms may go away)

Glucose 6-Phosphate Dehydrogenase Deficiency (G6PD Deficiency)

- Low G6PD (helps detox the cells) leads to high peroxides which causes cell lysis
- Oxidant exposure
- Bite cells (removal of Heinz bodies)
- Self limiting

Clinical Findings:

- Some asymptomatic, some episodic hemolysis
- Triggers: broad beans, drugs
- Spontaneous resolution
- Jaundiced sclera
- RBC's die because they can't reduce nasties, nasties attack hemoglobin bonds, heme breaks away from globin, globin denatures and sticks to RBC membrane (Heinz body) and spleen bites out Heinz bodies
-  

MAKE TOO LITTLE BLOOD

Too few bldg blocks:

Iron-Deficiency Anemia:

- GI bleeding is most important cause (not most common cause)
- Microcytic, hypochromic anemia (little cells with low hemoglobin)
- Must find out why (menstruation, child birth, colon cancer
- Atrophic glossitis (bald, shinny tongue with no papilla…need iron for that), Koilonychia (concavity in nail)

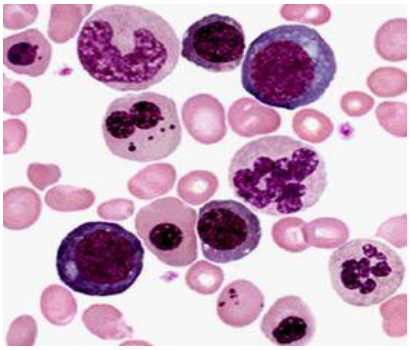
Causes: decreased iron intake (bad diet, bad absorption), increased iron loss (GI bleed worry most about, menses, hemorrhage), increased iron requirement (pregnancy)

ANEMIA OF CHRONIC DISEASE (can be confused with iron deficiency but in this case you cant metabolize iron correctly due to chronic disease)

- Infections, inflammation, malignancy
- Iron metabolism disrupted
- Normal looking cells
- Lab values low, anemia usually mild

MEGALOBLASTIC ANEMIA

- Defective DNA synthesis
- Nuclear/cytoplasmic asynchrony (different sizes)
- Low B12/folate
- Macrocytic anemia (MCV number high) with oval macrocytes and hypersegmented NEUTROPHILS
- Retarded DNA synthesis, unimpaired RNA synthsis = BIG cells, immature nucleus, mature cytoplasm
- Atrophic glossitis



Too few erythroblasts

APLASTIC ANEMIA

- Pancytopenia (everything decreased)
- Empty marrow (all fat and no hematopoetic tissue…just lymphocytes)
- Most idiopathic
- Causes: Idiopathic, drugs, viruses, pregnancy, Fanconi anemia (congenital disease)

Not enough room

- Bone marrow full of fibrosis

2: Benign Leukocytosis

Neutrophilia

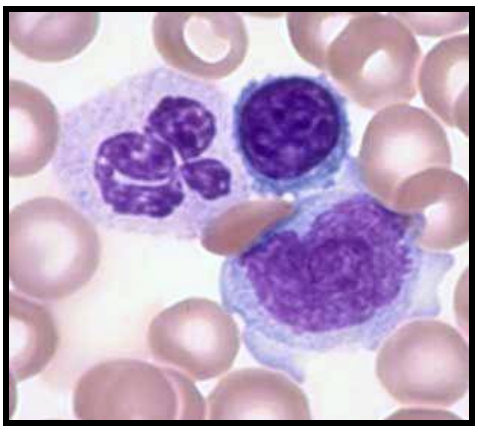
- Neutrophils fight infection, participate in inflammatory response, grow up and live in bone marrow, only 5% are in blood, normally only segmented neutrophils, half are marginated (cover around the vessel wall)
- Mature: segmented neutrophils
- Immature neutrophils (big blob of a cell)

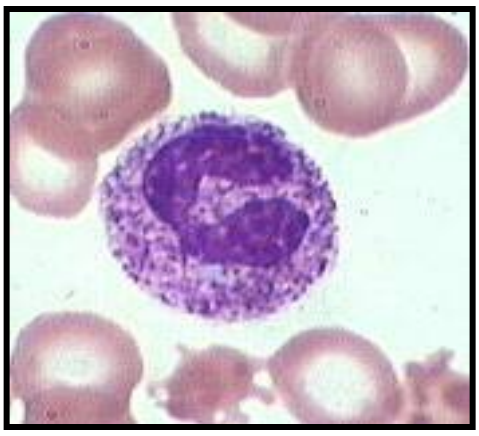
Causes of Mature Neutrophilia:

- Infection (bacterial)
- Inflammation
- Physical things (stress, hormones)

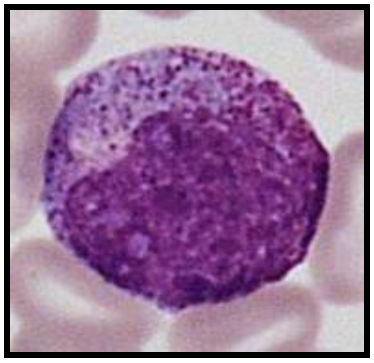
Toxic Changes:

- Seen only in infection
- 3 changes: toxic granulation, Dohle bodies (*dark blue/sky blue cause of RNA in cytoplasm*), cytoplasmic vacuolization (vacuoles that look like fat in cytoplasm, severe change, life threatening)
- Scariest: cytoplasmic vacuolization (left normal, right toxic)





Promyelocyte: just matures, won't divide, high concentration of granules



Causes of Immature Neutrophilia:

- Infection (bacterial)
- Inflammation
- Severe anemia
- Something filling up the marrow (can be bad)

3 Forms of Immature Neutrophilia:

- Left Shift (immature cells in the blood that shouldn't be there)
- Leukemoid Reaction
- Leukoerythroblastotic reaction
    - Due to something malignant or benign

Lymphocytosis

- Lymphocytes fight infection, participate in immunologic responses
- You'll have normal lymphocyte count! Varies a lot with age, bigger normal range in infants
- Normal immunophenotype in blood: T cell: 80%, B cell: 15%, NK cell: 5%

Types of Lymphocytosis: Mature and Reactive (funny looking)

Causes of Mature Lymphocytosis:

- Infectious lymphocytosis
- Bordetella pertussis (whooping cough)
- Transient stress

Causes of Reactive Lymphocytosis:

- Infectious MONO (Downey cells)
- Pediatric viral infection
- Viral Hep
- Immune disorders

Basophilia (BCML) BC…Mark's Love!

- ALWAYS due to CML (Chronic Myeloid Leukemia)

Eosinophilia

- Esi the SAD Parasite
- Skin disease, Asthma, Drugs, Parasite

Monocytosis (MIA)

- Infection, autoimmune disease, malignancy

3: Acute Leukemia

Hematologic Malignancies

Leukemia:

- Malignancy of hematopoietic cells
- Starts in the bone marrow, can spread to blood, nodes
- Myeloid or lymphoid
- Acute Leukemia:
    - Sudden onset, can occur in either kids or adults, fatal quickly without treatment, composed on immature cells (BLASTS)
    - Malignant proliferation of immature myeloid or lymphoid cells in the bone marrow cause by clonal expansion and maturation failure
    - Bad cause crowd out normal cells, inhibit function and attack into other organs
    - Symptoms of bone marrow failure are fatigue, infections, bleeding. Bone pain due to expanding marrow, organ infiltration (liver, spleen, brain)
    - Lab findings: blasts, leukocytosis, anemia, thrombocytopenia
- Chronic Leukemia:
    - Slow onset, ONLY adults, longer course, mature cells

Lymphoma:

- Malignancy of hematopoietic cells
- Starts in the lymph nodes, can spread to blood, marrow
- Lymphoid only
- Hodgkin (owl) or non-Hodgkin

Plasma cell disorders:

- Multiple myeloma (lots of plasma cells)

Diagnosis:

- Clinincal setting, morphology, immunophenotyping, molecular studies, cytogenetics
- Bone marrow biopsy
- Acute leukemias: mainly young cells, not many mature
- Chronic leukemias: a lot but look mature

AML Acute Myloid Leukemia

- Malignant proliferation of myeloid blasts in blood and bone marrow
- 20% cut off for diagnosis
- Many subtypes
- BAD PROGNOSIS

- AUER RODS (AML RODS)

M0 – M3 = Neutrophilic
M4 – M5 = Monocytic = brain involvement, gum involvment
M6 = RBC
M7 = Megakars (platelets)

Treatment of AML
- Chemo, bone marrow transplant

Prognosis
- Not good

Myelodysplastic Syndrome:
- Dysmyelopoiesis (cells look funny) and increased blasts
- May evolve into AML
- Usually older patients
- Asymptomatic or marrow failure
- Macrocytic anemia

ALL Acute Lymphoblastic Leukemia

- Malignant proliferation of lymphoid blasts in blood and bone marrow
- Classified by immunophenotype (B vs T)
- Common in children and prognosis is GOOD!
- T-lineage: bad
- B-lineage
    - B cell precursor ALL: better (most kids get this)
    - B cell ALL: bad (same thing as Burketts lymphoma) = starry sky pattern
- Prognosis: hyperdiploidy good!, under 1 and older than 10 bad, T is bad

4: Chronic Leukemia

CHRONIC MYELOPROLIFERATIVE DISORDERS:

- Malignant proliferation of myeoild cells (NOT blasts, but maturing cells) in blood/bone marrow
- 4 disorders: CML, PV, ET, MF
- Features common to all 4 disorders: occur only in adults, long clinical course, increase WBC with left shift, hypercellular marrow (stuffed wt cells), big spleen, Occurs only in adults, Long course

    - Chronic Myeloid leukemia (most common)

        Neutrophilic leukocytosis, basophilia, philli chromosome, 3 clinical phases

3 Phases:

- Chronic: 3-4 yrs, easily controlled, stable counts
- Accelerated Phase: dead in months, unstable counts
- Blast Crisis: now is acute leukemia, lots of blasts, dead in weeks

Treatment of CML: Gleevec

Prognosis: used to be 506 yrs but now who knows??

Polycythemia vera

High RBC, make blood sludgy, different from secondary polycythemia

Essential thrombocythemia

Very high platelet count in blood, different from secondary thrombocythemia

Myelofibrosis

Panmyelosis (all myeloid cells proliferating like crazy), marrow fibrosis, extramedullary hematopoiesis, teardrop cells (spleen gets huge)

CHRONIC LYMPHOPROLIFERATIVE DISORDERS:

- Malignant proliferation of lymphocytes in blood/bone marrow, many disorders, CLL most important, ONLY in adults, long course (indolent but incurable) Difficult to treat with chemo since not dividing often/regularly
- Chronic Lymphocytic Leukimea:
  - Small, mature lymphocytes, WEIRD: B cells but CD5+
  - Die usually from infection

5: Lymphoma and Myeloma

Lymphoma:

- Malignancy of hematopoitetic cells, starts in lymph nodes, spreads to blood, marrow. Lymphoid only. Hodgkin or non-Hodgkin.

Causes of Lymphadenopathy:

- Most common cause overall: benign reaction to infection
- Most common malignant cause: metastatic carcinoma

Non-Hodgkin Lymphoma:

- Malignant proliferation of lymphoid cells in lymph nodes, skips around, many subtypes, most are B cells
- Painless, firm lymphadenopathy, B symptoms weight loss, night sweats, fever
- Gingival/papaltal lesions
- LOW GRADE: older, incurable, small mature cells, non-destructive
- HIGH GRADE: children, aggressive, big ugly cells, destructive

Types of NHL

Low Grade:

Small Lymphocytic Lymphoma:

- Small mature lymphocytes, same thing as CLL, CD5+, long course, death from infection

MALT Lymphoma:

- Occurs in mucosa-associated lymphoid tissue, associated with Helicobacter pylori, early on can be treated with antibiotics.

Follicular Lymphoma:

- Small cleaved cells, grade 1,2,3, t(14:18) – IgH and bcl-2

Mycosis Fungoides / Sezary Syndrome:

- Skin lesions, blood involvement, cerebriform lymphocytes, T-cell immunophenotype

High Grade:

Diffuse Large-Cell Lymphoma:

- Large B cells, extranodal involvement, grows rapidly, bad prognosis

Lymphoblastic Lymphoma:

- Typical patient teenage male with mediastinal mass, lymphoblasts in diffuse pattern, same as ALL

Burkitt Lymphoma:

- Children, fast growing, starry-sky pattern, same as B-cell ALL

Hodgkins Lymphoma:

- Younger, contiguous spread, five suntypes, Reed-Sternberg cell, disease often localized, prognosis very good, danger is second malignacies

MULTIPLE MYELOMA:

- Malignant proliferation of plasma cells, monoclonal gammopathy, decreased normal immunoglobulins, osteolytic lesions
- Clinical features: weakness, infections, renal failure, bone pain, hypercalcemia
- Serum protein electrophoresis
- Treatment: chemo and radiation, bone marrow transplant, 5 yr survival with chemo only (20%)

6: COAGULATION

Pro-clotting:
Blood vessels constrict
Platelts form the plug
Fibrin seals up plug

Anti-clotting:
Cascade inhibition: TFP1, ATIII, Proteins C, S
Clot lysis: t-Pa (drug given to patients to open clot that works on plasminogen to plasmin which breaks down clot), plasmin (breaks down clot)

Coagulation Cascade:
Intrinsic: SIN

- Already in blood
- Factors: 8, 9, 11,12

Extrinsic: SEX

- Exposed TF first enters blood
- Factor 7 and TF

Final common pathway: X (ten) to Xa (meet me at ten)
Xa turns prothrombin into thrombin
Thrombin turns Fibrinogen to Fibrin to a clot

Co-factors (accelerators)
Factor 5 works with 10a
Factor 8 works with 9a
Protien C turns on cofactors
TFPI: Tissue Factor Pathway inhibitor acts on TF
ATIII (Heprin): acts on everything (bear hug)

Prothrombin Time: measures SEX
(order INR instead)
Increased PT = low 8, 10, 5, 2 ,1. Coumadin and Heparin, DIC

When to order INR test:

- To access liver function, monitor Coumadin therapy, diagnose DIC, access pre-op status

Partial Thromboplastin Time: measures SIN
Increased PTT = hemophilia A or B, DIC, heparin and Coumadin (both sides)
When to order PTT:

- Look at history of abnormal bleeding history, monitor Heparin therapy, diagnose DIC, pre-op status

Fibrin Degradation Product Assay:

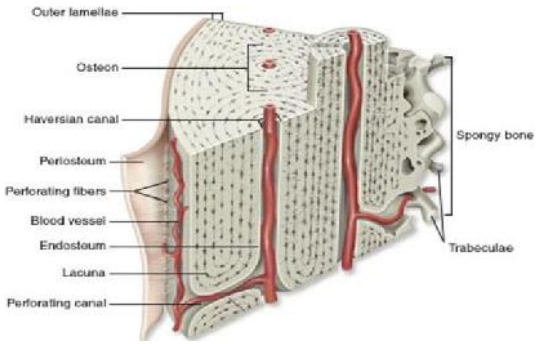
- Very sensitive, measures fibrin degredation products, not a specific test

D-dimers:

- Factor 13 is a crosslinker and d-dimers are formed when everything falls apart, more specific test, if patient neg…not clotting RULES OUT CLOT!

Increase FDP: Thrombi, minor clotting

Bone and Joint Pathology



Terminology

- Cortical bone – defines shape
- Cancellous bone – marrow
    - Mn, Mx, end of long bones in medullary canal
- Epiphysis – from subarticular plate to epiphyseal cartilage
- Metaphysis – area between epiphyseal plate to area where bone develops its funnel/flute shape
- Diaphysis – body of bone, between metaphyses
- Lamellar bone
    - Forms adult skeleton
    - Parallel arrangement of collagen fibers
    - Sparse osteocytes – uniform osteocytes in lacunae parallel to long axis of collagen fibers
- Woven bone
    - Irregular bone
    - Many osteocytes of various sizes/shapes
    - If in adults, usually pathological
- Osteoblasts – produce osteoid protein
- Osteocytes – osteoblasts within lacuna in bone
- Osteoclast – multinucleated, has Howship's lacunae for resorbing bone
- Cloaca – hole in bone during formation of draining sinus
- Sequestrum – fragment of necrotic bone in pus
- Brodie abscess – reactive bone from periosteum and endosteum, surrounds and contains infection
- Involucrum – periosteal new bone covering sequestrum

Bone Lesions

- Congenital lesions
    - Dysostoses, anplasia, supernumerary, dysplasias
- Hereditary lesions
    - Osteogenesis imperfect, achondroplasia, osteopetrosis
- Inflammatory
    - Osteomyelitis, fracture
- Metabolic
    - Osteoporosis, rickets, osteomalacia, hyperparathyroidism
- Neoplasms
    - Osteoma, osteochondroma, osteosarcoma, chondrosarcoma, Ewing's sarcoma
- Miscellaneous
    - Osteonecrosis, benign fibro-osseous lesions

Osteogenesis Imperfecta

- Collage I (α1 and α2 chain) defects
    - Dominant negative mutation – disastrous phenotype
    - Type I = normal lifespan
    - Type II = fatal
- Multiple fractures starting in utero
- Blue sclera – decreased collagen allows for visibility of underlying choroid (vascular) layer
- Dentinogenesis imperfect, conductive hearing loss

Achondroplasia (dwarfism)

- FGFR3 mutation
    - Constitutive activation, inhibition of chondrocyte proliferation
    - Thanatophoric dwarfism (missense mutation)
    - Absence or attenuation of zone of proliferative cartilage
- Epiphyseal disorder (plate closes prematurely preventing bone growth, affects ENDOCHONDROL ossification)
- Autosomal dominant, 80% are new mutations
- Normal mentation, average lifespan, normal head/torso
- Kyphoscoliosis (anterior/posterior lateral curvature)
- Cor pulmonale – respiratory abnormality causing right ventricular hypertrophy
- Hip problems – acetabulum deformity, narrowing of interpedicular distance

Osteopetrosis

- Reduced osteoclast-mediated resorbtion
    - Defective bone remodeling, reduced bone demineralization
    - Dense bone (marble/stone bone), unsound, brittle
- Recessive type – severe type, anemia, nerve entrapment, hydrocephalus (fluid accumulation inside the skull), infections, fractures
- Dominant type – milder
- Extramedullary hematopoiesis
- Wider metaphyseal and diaphyseal areas (looks like an Erlenmeyer flask)
- Extremely irregular bone with cartilage cores

Hereditary multiple osteochondromatosis

- Autosomal dominant
- Abnormality of epiphyseal plate (cartilage grows laterally to soft tissue), metaphyseal lesions
- Affects metacarpals, wrists, knees
    - Unequal extremity length
- Long term increased risk of chondrosarcome

Ollier's disease

- Start at metaphysis, becomes disaphyseal
- Multiple enchodromas – mature hyaline cartilage inside bone
- Small hand bones
- Chondrosarcoma present in 30-50% of cases

Myositis ossificans

- Reactive bone formation in muscle from injury
- Radiologically and histologically same as neoplasm
- Affects lower limbs

Fracture (bone discontinuity)

- Complete or incomplete, closed or compound, comminuted (spliter), displaced, pathologic, stress induced
- 3 phases
    - Inflammatory – first week
        - Rupture of blood vessels in periosteum and soft tissue
        - Bone necrosis at break site
        - Neovascularization peripheral to blood clot
        - PMNs, macrophages, other mononuclear cell involvement
        - Clot organization, early fibrosis
        - Callus formation – woven bone, some cartilage (which is eventually resorbed)
    - Reparative – months
        - Proliferating fibroblasts and osteoblasts
        - Blood clot resorbtion
        - Callus bridging
    - Remodeling – several weeks to years
        - Callus seals the bone ends
- Disruptions of Remodeling
    - Deformity (displacement)
    - Fibrous remodeling
    - Pseudoarthrosis
    - Infection, medications, systemic complications
    - Lack of Ca^{++}, P, vitD

Osteonecrosis

- Avascular, aseptic, ischemic death in absence of infection
    - Trauma
    - Emboli
    - Systemic diseases – sick cell anemia, lupus, gout, metabolic disorders
    - Radiation
    - Corticosteroids
    - Site specific – head of femur, navicular bone
    - Alcoholism
    - Osteochondritis dissecans – dead piece of cartilage

Osteomyelitis

- Inflammation of bone from infection
    - Staph, strep, E.coli, N.gonorrhea, H.influenza, salmonella, sickle cell anemia
- Direct penetration – wounds, fractures, surgery
- Hematogenous – bloodstream, teeth, metaphyses, knee, ankle, hip
- Complications – septicemia, acute bacterial arthritis, pathologic fracture, squamous cell carcinoma, amyloidosis (body synthesizes bad proteins), chronic osteomyelitis, tuberculous osteomyelitis (long bones, vertebrae), Pott's disease (tuberculous arthritis of the spine)

Osteoporosis

- Reduction of bone mass/unit bone volume
    - Metabolic bone disease
    - Bone displays normal ratio of mineral to matrix

Primary Osteoporosis

- Most common – reduced bone mass
- Uncertain etiology
- Common in post-menopausal women
- Elderly persons (senile)
    - Genetic – peak bone mass
    - Estrogens – decline
    - Aging
    - Calcium intake (at least 800mg/day)
    - Exercise
    - Environmental factors – smoking → decreased estrogen
- Osteopenia
- Decreased cortex thickness
- Reduced size/number trabeculae
- Fractures are a first sign
    - Compression fractures of vertebrae
- RANKL (RANK ligand) – receptor activator for nuclear factor kB (macrophages)
- RANKL and macrophage-colony stimulating factor (MCSF) – convert macrophage → osteoclast
- RANK-RANKL – regulated by osteoprotegerin (OPG)
- OPG-RANKL – curtails osteoclast formation (bone resorbtion)

- Menopause
    - Decreased serum estrogen
    - Increase IL1, IL6, TNF
    - Increased RANK/RANKL expression
        - Increased osteoclastic activity
- Aging
    - Decreased osteoprogenitor cell replication ability
    - Decreased osteoid synthesis
    - Decreased biologic activity of matrix-bound growth factors
    - Reduced physical activity

Secondary osteoporosis

- Corticosteroids – inhibition of osteoblast activity
    - Impairement of vitD dependent intestinal calcium absorbtion (secondary hyperparathyroidism)
- Hematologic malignancies
- Malabsorption – GI and liver disease
- Alcoholism – inhibition of osteoblasts, decreased Ca^{++} absorption

Osteomalacia and Rickets

- Inadequate mineralization of newly formed bone matrix
- Rickets – kids, epiphyseal plates open, problem with cartilage
    - Beaded appearance of costochondral junctions
    - Pectus carinatum
    - Dental abnormalities
- VitD deficiency (dependent)
- Phosphate deficienct (resistant)
- Defects in mineralization process
- Osteopenia
- Exaggeration of osteoid seams
- Poorly localized pain
- Femoral neck, pubic ramus, spine, ribs

Hyperparathyroidism

- Parathyroid adenoma, hyperplasia, rare malignancy
- PTH
    - Promotes phosphate excretion in urine
    - Stimulate osteoclast activity, tubular absorption, intestinal absorption – hypercalcemia
- Kidney stones
- Brown tumors (bone)
- Psychiatric depression (moans)
- GI tract irregularities (groans)

Secondary Hyperparathyroidism

- Renal osteodystrophy
- Chronic renal failure
    - Decreased phosphate filtration – hyperphosphatemia
    - Decreased VitD activation
    - Decreased Ca^{++} GI absorption – hypocalcemia

Paget Disease

- Bone modeling disorder
- 3 phases
    - Osteoclastic (hot)
    - Mixed – osteoclastic/osteoblastic
    - Burn out (cold)
- Skull involvement – cotton wool involvement, hypercementosis of the jaws
- Tests
    - Alkaline phosphatase
    - Urine hydroxyproline levels

Fibrous Dysplasia

- McCune Albright syndrome
- Jaffe syndrome
- Monostotic
- Ground-glass radiographic appearance

Bone Tumors

Bone Forming Benign

- Osteoma – face, skull, 40-50y/o, similar to normal bone
- Osteoid osteoma – metaphysis femur, tibia, 10-20y/o, woven bone involvement
- Osteoblastoma – vertebral column, 10-20y/o, similar to osteoid osteoma

Bone Forming Malignant (primary and secondary osteosarcoma – Paget's disease)

- Primary – metaphysis of distal femur, proximal, 10-20y/o, malignant cells produce osteoid
- Secondary – femur, humerus, pelvis

Benign cartilaginous

- Osteochondroma – metaphysis of long bones, 10-30y/o, bone and cartilage as a cup
- Chondroma – small bones of hands/feet, 30-50y/o, medullary cavity

Malignant cartilaginous

- Chondrosarcoma – femur, humerus, pelvix, 40-60y/o, within medullary cavity, malignant cells form cartilage (abnormal)

Other types

- Giant cell tumor – epiphysis of long bones, 20-40y/o, cortical lesions
- Ewing sarcoma (tumor) – diaphysis and metaphysis, 10-20y/o, medullary lesions, small round cells, t(11;20), FLI-EWS gene fusion

Periapical Cemento-osseous dysplasia and Florid Osseous Dysplasia

- Periapical region of Mn anteriors, associated with vital teeth
- African women 30-50y/o
    - Early lesion – radiolucent, could be granuloma or cyst
    - Mature lesion – mixed radiolucency
    - Late lesion – linear pattern radiolucency
- FOD – instead of just small lesion by localized teeth, covers 2 or more quadrants

Metastatic Tumors of the Jaws

- Most common form of cancer involving bone
- Likely metastatic from breast and prostate carcinomas (most common)
- >80% occur in Mn
- Pain, swelling, loose teeth, paresthesia
- Metastasis found in non-healing extractions
- Check site from which tooth was removed for local pain/mobility
- Irregular radiolucency (moth eaten appearance)
- Prognosis = poor, most patients die within a year

Osteoarthritis

- Most common joint disease
- Slow progressive degeneration of articular cartilage, narrowing of the joints
- Interphalangeal joints, knees, hips, cervical and lumbar spine
    - Weight bearing joints
    - Fingers
- Increased thickness of subchondral bone
    - Eburnated bone
- Osteophytes – fingers, distal interphalangeal joints
- Subchondral bone cysts (Haberden nodes)
- Primary – defect in cartilage, not inflammatory related
- Secondary – trauma, crystal deposits, infection

Rheumatoid Arthritis

- Systemic chronic inflammatory arthritis
- Autoimmune
    - Starts as a synovial disease
- Diarthrodial joints bilaterally
- 3 women per 1 man
- Remissions and exacerbations
- Hereditary, EBV correlated
- HLA Dw4 haplotype and related B-cell alloantigen
    - Genetically susceptible patient infection formation of Antibodies antibodies act as new antigen secretion of rheumatoid factor deposits of immune complexes in synovium activation of complement inflammation activation of macrophages T-cell homing secretion of cytokines
- Histologically has
    - Rice bodies
    - Hyperplastic synovium
    - Pannus
    - Allison-Ghormley bodies
    - Rheumatoid nodules

Spondyloarthropathy

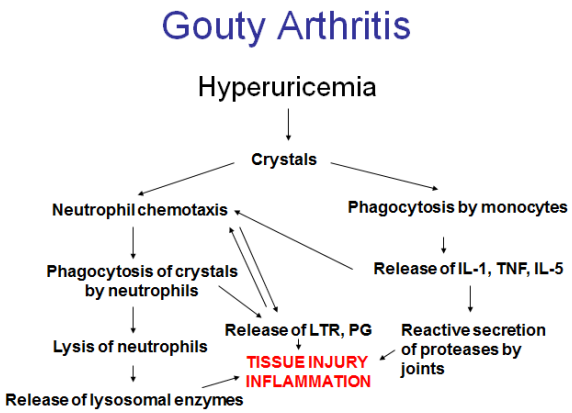
- Used to be a type of rheumatoid arthritis
- NOW comprises its own group of diseases
    - Ankylosing spondylitis – young men, vertebral column and sacroiliac joints
    - Reactive arthritis (Reiter's syndrome) – polyarthritis, conjunctivitis, non-gonococcal urethritis, oral lesion
    - Psoriatic arthritis
    - Arthritis and inflammatory bowel disease – Crohn's SV, ulcerative colitis

Juvenile Arthritis

- Still disease
- Children, females

Gout

- Increase serum uric acid, deposition of urate crystals in joints and kidneys
    - Only 15% of patients with increased uric acid have gout
        - Formation of granulomas with needle shaped crystals
        - Renal failure, urate stones
- Can result from purine overproduction
    - Heterocyclic organic compounds with organic ring attached to imidazole
    - Augmented nucleic acid metabolism
    - Decreased salvage of dietary purines and hypoxanthines
    - Decreased uric acid secretion
- Primary gout – hyperuricemia in absence of other disease
    - Asymptomatic hyperuricemia precedes gout
    - Impaired kidney secretion
- Secondary gout
    - Tumors – leukemias, lymphomas, after chemo
    - Alcoholism – accelerated ATP catabolism
- Acute gouty arthritis
    - Painful, unijoint precedes polyjoint
    - Podagra – painful, red metatarsophalangeal joint



- Tophaceous gout
    - Develop tophi – chalky, cheesy, yellow/white, pasty deposits of monosodium urate crystals
    - Deposits in helix and antihelix of the ear
    - Achilles tendon
- Treatments
    - Colchicine – prophylactic
    - Probenecid and sulfinpyrazone – interfere with urate resorbtion
    - Allopurinol – inhibits enzyme that converts xanthine and hypoxanthine into uric acid

Pseudogout

- Chondrocalcinosis – calcium phosphate crystals in hyaline and fibrocartilage
- Older individuals, no gender or race predilection, hereditary form has 30-60% prevalence
- Significant joint damage – knees, wrists, elbows, shoulders, ankles

Lyme Disease

- Ring-like rash at site of bite – erythema chronicum migrans
- Migratory joint pain and subsequent oligoarthritis

Bursitis (bursa is fluid cap between bone and muscle)

- Inflammation of bursa – elbow, shoulder, knee
- Fibrous thickening of bursa wall
- Tendency to doubt-fault in tennis, develop bad gold slide

Tumors/Tumor Like Conditions

- Ganglion cyst – wrist, CT cyst, near joint capsule or tendon sheath
- Synovial cyst – herniation of synovium through joint capsule (Baker cyst, popliteal fossa)
- Pigmented villonodular tenosynovitis – knee, hip, and/or ankle pain
- Giant cell tumor of tendon sheath – most common soft tissue tumor of the hand, painless mass often in wrist

Central Nervous System Pathology

Cells of the Brain

- Neurons – transmit impulses
- Astrocytes – part of blood-brain barrier
- Oligodendrocytes – produce myelin
- Microglia – phagocytic defense
- Ependymal cells – line ventricles

Cell Reactions to Injury

- Neurons – become red, degenerate
- Astrocytes – undergo hypertrophy, hyperplasia
- Microglia – proliferate
- Oligodendrocytes and ependymal cells – don't react much

Increased Intracranial pressure

- Cerebral edema
    - Generalized – diffuse insult, like hypoxia, toxin exposure, encephalitis, trauma
    - Focal – around focal lesions like acute infarcts, contusions, penetrating injuries, mass lesions
- Hydrocephalus – increased CSF fluid in ventricular system
    - Usually from impaired flow/resorbtion of CSF (rarely overproduction)
    - If infancy, enlarges head
    - If after infancy, ventricular expansion and ICP increase
    - 3 types
        - Non-communicating – block in ventricular system, only a portion of ventricular system enlarged
        - Communicating – block in subarachnoid space, entire ventricular system enlarged
        - Ex vacuo – ventricular system dilated from brain atrophy (compensatory increase in CSF volume)
    - Feared outcome – herniation
        - One part of brain pushed into another compartment
        - Symptoms – headache, vomiting, decreased consciousness, papilledema, limited ocular ability
        - Often fatal
- Expanding mass lesions

Vascular disorders

- Global cerebral ischemia
    - Caused from hypotension
    - Outcome dependent on hypotension severity
        - Mild – transient confusion
        - Severe – persistent vegetative state, brain death
    - "watershed" infarcts
- Focal cerebral ischemia
    - Caused from blood flow obstruction
    - Hemorrhagic (red) infarcts – from emboli and reperfusion, often arise from the heart
        - Bleeding out
    - Ischemic (pale) infarcts – from thrombi, often arise in atherosclerotic plaques
        - Total flow obstruction
    - Transient ischemic attacks (TIAs) – often harbingers

- Trauma
    - Skull fractures
        - Displaced if bone is depressed
        - Falls while awake usually occipital
        - Falls if unconscious usually frontal
        - Basal skull fractures have unique symptoms
            - Lower cranial nerves affected
            - Orbital or mastoid hematomas distant from impact site
            - CSF draining from ear or nose
    - Concussion
        - Altered consciousness from head injury due to change in head momentum
        - Unknown mechanism
        - Amnesia, confusion, headache, visual disturbances, nausea, vomiting, dizziness
        - Grading scheme
            - Grade 1 – no loss of consciousness, lasts <15min
            - Grade 2 – no LoC, lasts >15min
            - Grad 3 – LoC
        - Post-concussive neuropsychiatric syndromes exist (especially for repetitive injuries)
    - Direct parenchymal injury
        - Contusion (bruising)
        - Laceration (tissue tear)
        - Blows can result in coup (contusion at contact) or countercoup (contusion opposite side) injuries
    - Diffuse axonal injury
        - Injury to axons in deep white matter of brain
        - Twisting/shearing of axons leading to cell death
        - Can be caused by angular acceleration alone
            - Shaken baby syndrome
        - Common cause of coma after trauma
    - Traumatic vascular injury
        - Epidural hemorrhage
            - Blood above dura, tear in middle meningeal artery, neurosurgical emergency
        - Subdural hemorrhage
            - Blood between dura and arachnoid, shearing of bridging veins
            - Acute (hours) or chronic (months)
        - Subarachnoid hemorrhage
            - Blood in subarachnoid space
            - Contusions, ruptured berry aneurysms
            - Neurosurgical emergency

- Infections
    - Meningitis
        - Inflammation of meninges
        - Symptoms – fever, headache, stiff neck
        - Without treatment – loss of consciousness, coma, death
        - Cause
            - Bacterial
                - Newborns – E.coli, S.agalactiae
                - Young adult – N.meningitidis
                - Elderly – S.pneumonia
            - Viral – coxsackie, ECHO, mumps
            - TB (rarely)
    - Encephalitis
        - Inflammation of brain substance
        - Symptoms – seizures, confusion, delirium, coma, reflex asymmetry, ocular palsies, altered mood, altered memory, altered behavior
        - Cause
            - Viruses – arbovirus, HSV1 and 2, CMV, rabies, HIV
    - Abscess
        - Routes – direct implantation, local extension, hematogenous spread
        - Predisposing factors – endocarditis, congenital heart disease, chronic pulmonary infections
        - Causative bacteria – S.viridans, Staph.aureus
        - Progressive focal deficits + signs of increased ICP
    - Prion disease
        - Abnormal fold of cellular protein (PrP)
            - Both transmissible and infectious
        - Creutzfeldt-Jakob, kuru, scrapie, mad cow
        - Causes spongiform change (intracellular vacuoles) in neurons and glia
        - Symptomatic progressive dementia

- Tumors
    - Metastases more common than primaries
        - Lung
        - Breast
        - Melanoma
    - Primary tumors classified by cell origin
        - Glioma (glial cells)
            - From astrocytes, oligodendrocytes, ependymal cells
            - Often fatal (location and infiltrative borders prevent complete excision)
            - Glioblastoma (highest grade astrocytoma) most malignant
        - Medulloblastoma (primitive neurons)
            - Tumor of primitive neurons
            - Located in cerebellum
            - Usually in children
            - Very radiosensitive
        - Menongioma (meningeal cells)
            - Encapsulated benign tumor
            - Surface of brain (no penetration)
            - Symptoms caused from compression
            - Cured via resection
        - Nerve sheath cells
            - Arise from cranial (especially CN VIII) and spinal nerve roots, peripheral nerves
            - Derived from support cells of nerves
            - Benign, but may compress nerve
            - Schwannoma (verocay body) – “acoustic neuroma” if involving CN VIII
            - Neurofibroma, may lead to neurofibromatosis
- Demyelinating disease
    - Multiple sclerosis
        - Most common demyelinating disorder
        - Unknown etiology, autoimmune related
        - Variety of motor and sensory symptoms
        - Relapse-remitting recourse
        - Plaques (areas of demyelination) in brain and spinal column
    - Guillain –Barre syndrome
        - Acute peripheral neuropathy
        - Progressive, ascending weakness
        - Usually self-limiting (may involve respiratory muscles – requires respiratory intensive care)
        - Autoimmune attack on peripheral nerve – demyelination and conduction blockage

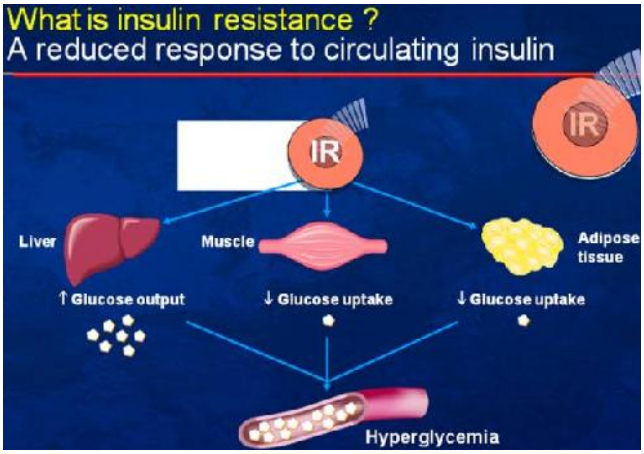
- Degenerative disease
    - Alzheimer's disease
        - Most common form of dementia in elderly
        - Symptoms
            - Early – forgetfulness, memory disturbance
            - Middle – language deficit, loss of learned motor skills, alteration in mood/behavior, disorientation
            - Late – profoundly disabled, mute, immobile
        - Gross histology – cortical atrophy, neuronal loss
        - Microscopic histology – neurofibrillary tangles, neuritic plaques
    - Parkinson's disease
        - Degeneration of pigmented neurons (contain dopamine) in substantia nigra
        - Unknown etiology
        - Symptoms
            - Early – tremor, rigidity, slow movement
            - Late – cognitive problems, dementia, dyskinesia
        - Gross histology – atrophy of substantia nigra
        - Microscopic histology – Lewy bodies (inclusions in neurons)
    - Huntington Disease
        - Degeneration of basal ganglia and cerebral cortex
        - Autosomal dominant
        - Begins 30-40 y/o, 10-20 year progression
        - Symptoms
            - Early – lack of coordination, unsteady gait
            - Late – chorea (involuntary writhing), psychiatric symptoms, dementia
    - Amyotrophic Lateral Sclerosis
        - Degeneration of neurons involved in motor control
        - Rapidly progressive weakness, muscle atrophy, spasticity, dysphagia
        - Symptoms
            - Early – myalgia in arm/leg, twitching, slurred speech
                - Death within 2-3 years from respiratory compromise
        - Sensory and cognitive functions unaffected

Diabetes

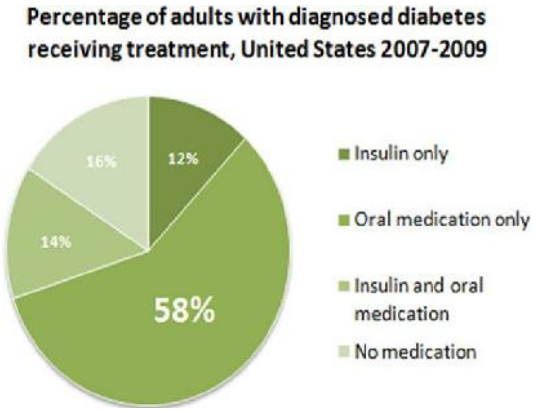
- Group of diseases characterized by high sugar glucose
    - Can lead to serious health problems, premature death
- Cardiovascular disease – leading cause of diabetic death
    - 70% patients die of heart disease/stroke (2-4x higher than normal)
    - 67% have high BP (>140/80)
    - Smoking doubles risk of heart disease
- Diabetes leading cause of
    - Renal failure
    - Adult blindness
    - Nontraumatic lower limb amputations
- Perio risk increase 2-3x for diabetics
- 60-70% diabetics have neuro damage
    - 30% of >40y/o have impaired lower limb sensation
    - 2x more likely to have depression
- Type 1 – autoimmune (kids, young adults)
    - Body destroy pancreatic beta cells (insulin secretion)
    - 5% of cases, no prevention
- Type 2 – insulin resistance (adults)
    - Obesity, family history, gestational diabetes, impaired glucose metabolism, physical inactivity, ethnicity
    - Africans, Hispanic/Latinos, Indians, some Asians, Natives, Pacific Islanders
    - 95% of cases
- Gestational Diabetes
    - Diagnosed during pregnancy
    - Affects 7% of pregnancies
    - 5-10% of women with gestational diabetes diagnosed with Type 2 after pregnancy
    - 35-60% women with gestational diabetes develop diabetes within 10-20 years
- 25.8M people have diabetes (8.3% of USA population)
        - 18.8M diagnosed (75%)
        - 7.0M undiagnosed (25%)
    - 20-44y/o – 3.7% have diabetes
        - 1.9M new cases in <20y/o in 2010
    - 45-67y/o – 13.7% have diabetes
    - >65y/o – 26.9% have diabetes

    - 16.1% Native American have diabetes
        - 3.5% of Alaskan Natives
        - 33.5% of South Arizona Natives
    - Blacks 77% high risk of diabetes than Whites
        - 18.7% Blacks have diabetes
    - 11.8% Latinos have diabetes
        - 13.3% Mexicans
        - 7.6% Central/South Americans and Cubans
        - 13.8% Peurto Ricans
    - 8.4% Asians have diabetes

- 215K young adults have diabetes
    - Usually Type 2, except in Native American Youth
    - Type 2 usually rare in those <10y/o
        - 97% are Type 1
        - Most common in whites
    - Higher rates of Type 2 in minority races
        - 81% are Type 1
        - Type 2
            - 6% in whites
            - 76% in American Indian Youth



- Ever 24h
    - 5K new cases
    - 180 diabetes have amputations
    - 133 begin end stage renal treatment
    - 634 die related to diabetes
- Preventing Diabetes Complications
    - Blood glucose control
    - Blood pressure control
    - Blood lipid control
    - Preventative care for eyes, kidneys, feet, teeth, gums



Endocrinology Pathology

Organs	Diseases
- Pituitary - Thyroid - Adrenals - Pancreas	Non-Neoplastic - Too much hormone - Too little hormone Neoplastic - Benign - Malignant

Pituitary

Anterior pituitary (adenohypophysis)	Posterior pituitary (neurohypophysis)
- Secretes GH, ACTH, TSH, LH, FSH, prolactin - Hypothalamus controlled - Most problems occur here	- Secretes oxytocin, ADH - Hypothalamus makes these - Neurohypophysis stores them

- Oxytocin – labour, milk letdown, cuddling (after orgasm), monogamy (vole studies), trust (investment experiment), female bonding (UCLA study)

Disorders

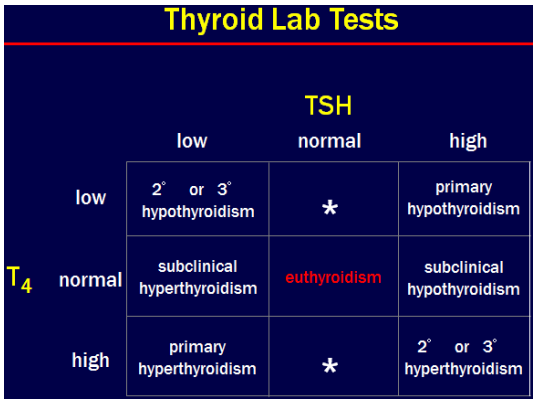
- Hyperpituitarism – too much ANTERIOR pituitary hormones (adenohypophysis)
    - Most common cause – pituitary adenoma
        - No symptoms endocrine abnormalities mass effects
        - Pituitary tumor can bulge into sphenoid sinus – endoscopic removal through sella turcica
    - Many types
        - Growth hormone adenoma

Clinical Findings	Lab Findings
- Diabetes mellitus - Hypertension - Arthritis - GI carcinoma	- Increased GH (spurts) - Increased IGF-I (better) - GH unresponsive to glucose

        - Acromegaly
            - Changes structures over time
            - Prominent forehead, brow ridge, mandibular protuberance
            - Facial changes
            - Pseudoedema
        - Prolactinoma
        - ACTH producing adenoma
        - FSH/LH producing adenoma
        - TSH producing adenoma
        - Non-functioning adenoma
- Hypopituitarism
    - Causes – pituitary destruction, ischemic necrosis, pituitary apoplexy
        - Dwarfism
        - Libido loss, menstrual abnormalities
        - Hypothyroidism
        - Adrenal insufficiency
    - Panhypopituitarism is very rare because the pituitary has a huge reserve

Thyroid

- 3^o (TRH) 2^o (TSH) 1^o (thyroid growth & hormone synthesis)
- Most thyroid hormone is bound (inactive), only free form is active
- Thyroid hormone
    - Binds to nuclear receptors
    - Changes gene expression
    - Increases carb and fat breakdown
    - Stimulates protein synthesis
- Result – increased basal metabolic rate



Disorders

Hyperthyroidism – increased TH hypermetabolism	Hypothyroidism – decreased TH hypometabolism
- Cardiac – rapid pulse, arrhythmias - Neuromuscular – tremor, emotional lability - Eye – lid lag - Skin – warm, moist - GI – diarrhea - Skeletal – osteoporosis - Thyroid storm – massive increase in TH	- Slowing of mind and body - Myxedema – deepened voice - Cardiac – slow pulse - GI – constipation - Skin – dry, cool, pale - Cold intolerance - Delayed reflexes - Myxedema coma
Congenital hypothyroidism	
- Iodine deficiency, genetics - Symptoms range from mild to severe - Treatment – TH replacement - Prevention is better – take in iodized salt	

Thyroiditis – inflammation of the thyroid

Hashimoto's thyroiditis	DeQuervain thyroiditis
- Most common cause of thyroiditis in USA - F>>M - Autoimmune destruction of gland - Hurthle cells, myxedema	- Recent URI - Self-limiting – looks scary, but is actually harmless and goes away by itself - Multinucleated giant cells
Lymphocytic thyroiditis (silent thyroiditis)	Fibrosing thyroiditis
- Post-partum or middle aged - Mild symptoms – silent, does not cause problems, lymphoid infiltrate	- Rock-hard neck mass - Can compress trachea - Reidel thyroiditis

Graves Disease	Goiter – general term for big thyroid

- Common autoimmune disease
- Triad
  - Hyperthyroidism
  - Ophthalmopathy - exophthalmos
  - Dermopathy – pretibial myxedema
- Anti-TSH receptor antibodies
  - Stimulate thyroid growth
  - Cause T_4 release
  - React with retro-orbital tissues, skin of legs
	- Defective T_4 synthesis – enlarged thyroid gland to compensate
	  - Iodine deficiency (endemic)
	  - Other defects (sporadic)

Thyroid Neoplasms

- Usually present as nodules
- Usually benign – thyroid carcinoma is uncommon
    - Test – biopsy or FNA
        - Cancer – take it out
        - Follicles – take it out
        - Thyroiditis – treat it
- Thyroid ademoma
    - Common
    - Mostly euthyroid (some are hyperthyroid)
    - Radioactive iodine uptake – most adenomas are "cold"
    - Take it out – need to see whole tumor (including capsule) to make sure it's not carcinoma
- Thyroid carcinoma

Papillary carcinoma (80%)	Follicular carcinoma (10%)	Medullary carcinoma (5%)	Anaplastic carcinoma (<5%)
Best prognosis "Orphan Annie" tumor - Nuclei resemble her eyes Affects younger women Size remains static for years Usually non-fatal Psammoma bodies - Named after Annie's dog "Sandy"	Good prognosis	Rare Endocrine tumor Bad prognosis	Rare Bulky, fast growing Metastatic at diagnosis Very bad prognosis

Adrenal Cortex

- Glomerulosa – salt
- Fasiculata – sugar
- Reticularis – sex
    - GFR gets sweeter as you go lower

Cushing's Syndrome – too much cortisol and glucocorticoids

Causes		Symptoms	
- Ingested steroids - Adrenal adenoma - Pituitary adenoma - Paraneoplastic adenoma		- Hypertension, weight gain - Characteristic habitus - Buffalo hump, frontal belly, edema face - Glucose intolerance	
Pituitary Cushing Disease	Adrenal Cushing syndrome	Paraneoplastic Syndrome	Iatrogenic cushing synd
Tumor in adenohypophysis Increased ACTH secretion Increased cortisol secretion	Tumor in cortex or Nodular hyperplasia Increased cortisol	Lung cancer Increased ACTH secretion Increased cortisol secretion	Steroids Adrenal atrophy Intaking cortisol

Addison Disease – too little cortisol and mineralcorticoids

- Primary chronic adrenal insufficiency - Usually autoimmune - Treat with Na^+ IV, hydrocortisone, dextrose	- Slow onset (90% of cortex needs to be destroyed - Weakness, fatigue, GI complaints - Hypotension, brain swelling - Skin hyperpigmentation (bronzing) - Salty good cravings, vomiting, vision loss

Waterhouse-Friderichsen Syndrome

- N. meningitides (bacterial infection)
- Hypotension, shock
- DIC
- Massive bilateral adrenal hemorrhage
- Rapidly progressive

Pheochromocytoma

- Neoplasm of catecholamine-producing cells
- Rare cause of hypertension
- Urine has catecholamines, VMA, metanephrines
- The 10% tumor – 10% extra-adrenal, 10% bilateral, 10% familial (MEN), 10% malignant

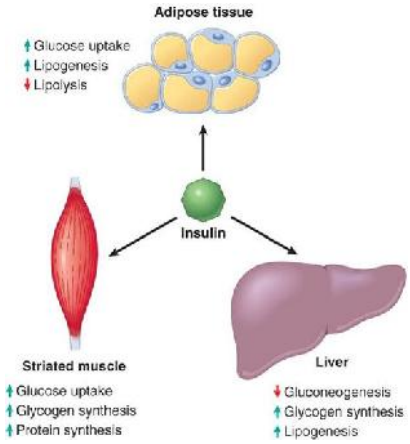
Neuroblastoma

- Neural crest cell derived
- Relatively common childhood tumor
- Prognosis is better if
    - o <1.5 y/o
    - o Lower stage/grade tumors
    - o Hyperdiploid tumors
    - o Fewer copies of N-myc gene

Diabetes (insufficient insulin)

- 100m worldwide (3% of humans) - 13m USA (only half diagnosed) - 54K die/year in USA (#7 cause of death) - Lifetime risk of getting diabetes = up to 5%	Disease in which body does not produce or properly use insulin Primary vs secondary Primary – type 1 vs type 2 Pathogenesis is different, end result is the same

Type I	Type II
- Not enough β-cells - Lots of susceptibility genes, one in MHCII region - MHC II antigen is abnormal - T-cells attack islet cells (slow persistent attack)	- Can't make enough insulin, tissues can't use insulin properly - Probably lots of contributory genes - Deranged insulin secretion - Insulin resistance



- Diabetes Pathophysiology
    - o Non-enzymatic glycosylation
        - Glucose attaches itself to proteins, forms AGEs
            - AGE = advanced glycosylation end products
        - AGEs crosslink, trap stuff
        - AGEs bind to receptors, do nasty stuff
    - o Intracellular hyperglycemia
        - Some cells take up glucose without insulin
        - Glucose activates protein kinase C
        - … which induces production of pro-angiogenic and pro-fibroblastic molecules

- Diabetes Complications
    - Increased infections
        - Oral candidiasis
        - Malignant Otitis externa
    - Microangiopathy
        - Accelerated, severe atherosclerosis
        - Increased permeability
    - Retinopathy
        - Retinopathy
        - Cataracts
        - Glaucoma
    - Nephropathy
        - Glomerular lesions
        - Vascular lesions
        - Pyelonephritis
        - Fungal bladder infections
    - Neuropathy
        - Peripheral neuropathy
        - Motor, sensory neuropathy

MEN Syndromes

- Genetic disorders - Predisposition to endocrine tumors - MEN-1 and MEN-2	MEN tumors - Younger - Multiple organs - Multifocal - Hyperplasia - Aggressive

MEN-1 – other endocrine organs	MEN-2 – thyroid
Parathyroid hyperplasia Pancreatic carcinoma Pituitary adenoma Other stuff - Mutation in MEN1 gene – classic tumor suppressor - MEN1 encodes menin - Run of the mill - Inactive	Medullary thyroid carcinoma Pheochromocytoma Parathyroid C-cell hyperplasia Other stuff - RET mutation o Proto-oncogene oncogene o Tyrosine kinase receptor o Constitutively (always) activated o Unusual! - Genetic testing required

Muscle Pathology

Duchene muscular dystrophy

- X-linked – deletion of gene that encodes dystrophin
- Pelvic and shoulder girdles
- Degeneration of muscles, impaired repair, fibrosis, fibrofatty deposits
- Elevated serum creatinine kinase
- Death from respiratory insufficiency, cardiac arrhythmia, can be wheelchair bound at 10-15y/o

Myotic dystrophy

- Autosomal dominant, Chr 19
- Most common form of adult muscular dystrophy
- Progressive muscular contractions rigidity
- Atrophy of Type I fibers, hypertrophy of Type II fibers
- Anticipation – progressively earlier age of onset, increased severity in successive generations
- 3 clinical groups
    - Congenital
    - Adult – facial and jaw muscles, ptosis
    - Late – minimal symptoms

Autoimmune Myopathies

- Dermatomyositis – complement mediated cytotoxic antibodies against muscle microvasculature
- Polymyositis – direct damage by cytotoxic T-cells ($CD8^+$)
- Myasthenia Gravis – muscle fatigue from circulating antibodies against ACH receptor at myoneural junction
    - Extraocular muscles, swelling muscles, extremities
    - Patients can develop other autoimmune diseases
    - 40% have thyomoma
    - 75% of remaining have hyperplasia
    - Removal of thymus can be curative

Polyarthritis Nodosa

- Men
- Vasculitis of small and medium sized arteries
- Decreased blood supply to organs
- Correlation to Hep B (30%), sulfa drugs, penicillin

Polymyalgia Rheumatica

- Pain and stiffness around large muscle groups
    - Neck, shoulders, hips

Temporal arteritis

- Inflammation of large arteries
    - Temporal artery, other arteries
- Headache, visual changes
- Confirmation via biopsy
- If untreated, can lead to blindness

Female Reproductive

Cervix

- Cervical carcinoma
    - No longer in top 10 (used to be most common)
    - Decrease due to pap test
    - Precursor lesions are increasing (early detection)
- Cervical intraepithelial neoplasia (CIN)
    - Precursor for carcinoma
    - Almost all carcinomas arise from CIN, but not all CIN become carcinomas
    - 3 grades – low grade dysplasia = CIN I and II, high grade = CIN III
        - CIN I – mild dysplasia – 50% regress, 20% progress
        - CIN II – moderate dysplasia
        - CIN III – severe dysplasia – 30% regress, 70% progress
    - Risk Factors
        - Early age first intercourse
        - Multiple sex partners
            - Male partner with multiple previous partners
        - Persistent infection with "high risk" HPV
        - Smoking, immunodeficiency
- Cervical Carcinoma and HPV
    - Detectable in almost al CIN and cancer
    - "high risk" HPV types
        - 16, 18, 45, 31 – found in carcinomas, integrate into genome inactivate p53 and Rb
    - "low risk" HPV types
        - 6, 11 – found in condylomas (benign), do not integrate into genome
    - Transformation zone = regrowth of squamous epithelium
- Invasive cervical carcinoma
    - Usually squamous, arising from CIN
        - A few are adenocarcinomas
    - Around 45y/o (10-15y after CIN developes)
    - Slow spread, most cases diagnosed early
    - Mortality related to stage
        - Stage 0 – preinvasive – 100% survival after 5 years
        - Stage 4 – 10% survival after 5 years

Uterus

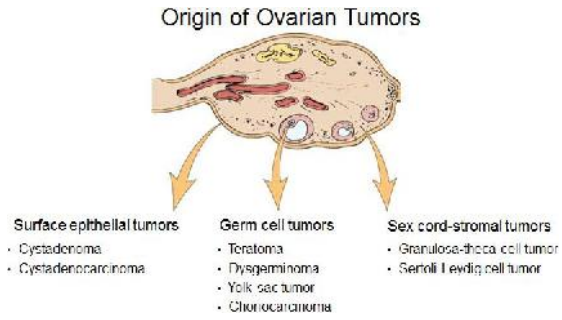
- Endometriosis
    - Location of endometrial glands outside uterus
        - Usually in the peritoneum, rarely in lymph nodes
    - Endometrium undergoes cyclical bleeding
        - Results in scarring, pain, sometimes sterility
    - Endometrium may get out via
        - Regurgitation through fallopian tubes – endometrium in ovary = chocolate cyst
        - Lymphatic dissemination
        - Extrapelvic dissemination via pelvic veins
- Endometrial hyperplasia
    - Proliferation of endometrium due to excess estrogen
    - Risk factors – anovulatory cycles, obesity, estrogen producing ovarian tumors, exogenous hormones
    - 3 categories
        - Simple
        - Complex
        - Atypical
    - More severe hyperplasia = increased carcinoma risk
- Endometrial sarcoma
    - Not before 40y/o, peak age = 55-65y/o
    - Frequently from endometrial hyperplasia
    - Risk factors = obesity, nulliparity, estrogen replacement
    - Symptoms – leucorrhea, irregular bleeding
    - Metastasizes late
- Leiomyoma
    - “fibroid” – benign tumor of smooth muscle
    - Very common
    - Stimulated by estrogen
    - Menorrhagia, metrorrhagia, or asymptomatic
- Leiomyosarcoma
    - Malignant tumor of smooth muscle
    - Necrotic, atypical cells and lots of mitoses
        - Often occurs after surgery
    - Many metastasize, especially to the lungs
    - 40% survival after 5 years

Ovaries

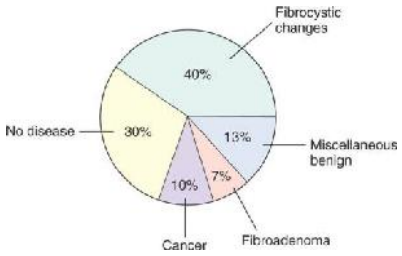
- Cystademona
    - Benign tumor derived from surface epithelium
    - Repeated ovulation, scarring, infolding of epithelium leads to cysts which undergo neoplastic transformation
    - Typically large, occasionally bilateral (really abnormally big large belly)
- Teratoma
    - Benign tumor with differentiation along all 3 germ layers (ectoderm, mesoderm, endoderm)
    - Usually cystic with skin inside (dermoid cyst)
    - Sebaceous material, matted hair, teeth, bone
    - Malignant variant has immature tissues
- Ovarian cancer
    - 23K new cases, 15K deaths in 2007
    - 5th commonest, 5th deadliest cancer in women
    - No definitive signs until late stage
    - Peak age = 50y/o
    - Most are cystadenocarcinomas
    - Symptoms – feelings of fullness/bloating, pelvic and back pain, abnormal menses
    - Risk factors – nulliparity, genetics (BRCA gene mutation), NOT using oral contraceptives
    - Treatment – surgery, radiation, chemotherapy
    - Prognosis – stage dependent

        Confined to ovary – 70% survival after 5 years

        Through ovarian capsule – 13% survival after 5 years



Breast



- Many breast diseases present as lumps
- Most lumps represent benign things, but always needs to be evaluated
  - Ultrasound, mammography, fine needle aspiration, and biopsy

- Fibrocystic change (NOT fibrocystic disease)
  - 2 types
    - Nonproliferative – increased stroma, dilation of ducts, formation of cysts
    - Proliferative – hyperplasia of breast epithelia (if shows atypia, 5x increased risk of cancer)
  - Cause – exaggeration of normal breast cycles
  - Very common, present in most women at autopsy – rarely associated with increased cancer risk
- Fibroadenoma
  - Most common benign breast tumor
  - Stimulated by estrogen
  - Peak = 20s
  - Solitary, discrete, moveable mass
  - Fibrous tissue with compressed ducts and lobules
- Breast carcinoma
  - 180K new cases, 40K deaths in 2007
  - Most common, 2nd most deadly cancer in women
  - Lifetime risk = 1/8
  - 75% patients >50y/o
  - Rate was increasing, now stable
  - Risk factors – age, family history, increased estrogen exposure, obesity, alcohol, high fat diet
    - 5-10% are hereditary – worry if 1st degree relative has/had breast cancer
      - Most carriers have cancer by age 70
    - BRCA1 or BRCA2 mutations – tumor suppressor genes, help with DNA repair
    - Difficulties with genetic testing
  - Clinical findings
    - Palpatory discovery
      - Solitary, painless, moveable mass 2-3cm diameter
      - Axillary nodes positive in 50% of patients
    - Mammography discovery
      - 1cm in size
      - Axillary nodes positive in 15% of patients
    - As disease progresses
      - Fixation to chest wall, adherence to overlying skin
      - Peau d'orange (looks like peal of an orange skin)
  - Histological Types
    - Non-invasive
      - Ductal carcinoma in situ (DCIS)
      - Lobular carcinoma in situ (LCIS)
    - Invasive
      - Ductal, lobular, inflammatory, others
  - Prognostic factors
    - Size of tumor, lymph node involvement, distant metasteses, tumor grade, tumor histology

TNM staging system for breast cancer

Overall stage	T	N	M	5y survival
Stage 0	DCIS	0	M0	92%
Stage I	<2 cm	0	M0	87%
Stage II	<5 cm	<3	M0	75%
	>5 cm	0	M0	
Stage III	<5 cm	4+	M0	46%
	>5 cm	1+	M0	
	Any T	10+	M0	
	Any T	Any N	skin or chest wall	
Stage IV	Any T	Any N	M1	13%

Male Reproductive

Testis

- Cryptorchidism
    - Incomplete testicle descent into scrotum
    - 3% of newborns, most descend within 6 months
    - Associated with male sterility, malignancy
    - Orchiopexy may decrease risk (or just allow earlier detection)
- Testicular Cancer
    - Most common cancer in men 15-35 y/o
        - 5 per 100K males
    - Firm, painless enlargement of testis
    - Seminomas and non-seminomas
        - Some present with metastases
    - Curable if detected early
        - Diagnostics – small painless lump, enlarged testicle, feeling of heaviness in testicle or groin, fluid accumulation, change in the way testicle feels
    - Seminoma
        - Half of all testicular cancers
        - Arise from germinal epithelium of seminiferous tubules
        - "spermatocytic" variant occurs in older patients – better prognosis
    - Non-seminoma
        - Embryonal tumor – undifferentiated stem cells
        - Yolk sac tumor – yolk sac cells
        - Choriocarcinoma – immature placental cells
        - Teratoma – somatic tissue cells
    - Tumor markers
        - Important for staging and followup
        - hCG – normally made by placental cells, increased in choriocarcinoma, increased in seminoma
        - α-ferroprotein – normally made by fetal yolk sac, increased in yolk sac tumors and embryonal carcinoma
    - Treatment
        - Overall good prognosis – early detection = 90% survival, 8K new cases only 400 deaths/year
        - Seminomas – often localized but large
            - Metastasize locally, then laterally, then distantly
            - Highly sensitive to radiation and chemo
        - Nonseminomas
            - Metastasize earlier and farther out
            - Worse prognosis

Prostate

- Nodular hyperplasia
  - Very common – 90% of men have by their 70s
  - Symptomatic urinary obstruction
    - Big prostate, usually affects central zone of prostate
    - Symptoms (10% of patients) – hesitancy, urgency, nocturia, poor urinary stream
  - Benign proliferation of glands and stroma
  - Caused via excessive androgens
- Prostate cancer
  - Most common cancer in men, 2nd deadliest
  - Peak incidence = 65-75y/o
  - Often asymptomatic – detected via PSA test
    - Prostate Specific Antigen test – enzyme made by prostatic epithelial cells
      - PSA <4 = normal, >10 suggests cancer
        - Can be elevated in benign tumors – questionable screening usefulness
    - Early – asymptomatic
    - Later – hard nodule via rectal exam
    - Much later – local pain, obstructive symptoms
  - Usually affects peripheral zone of prostate
    - Most are adenocarcinomas
  - Causes
    - Hormonal – males castrated before puberty don't get carcinomas
      - Treatment with estrogens/orchiectomy is curative
    - Genetics – increased risk with first-degree affected relatives, earlier onset in blacks
    - Environmental – increase in Scandanavian countries, decrease in asia
      - Correlation to high animal fat diet
  - Treatment and prognosis stage dependent
    - Better differentiated = better prognosis
    - Treatment = surgical, radiation, hormonal therapy
      - Limited disease = 90% survival over 10 years
      - Metastatic disease = 10-40% survival over 10 years

Neoplastic Skin Pathology

Benign tumors

- Nevus (mole)
  - Benign proliferation of melanocytes
  - Junctional – at dermal-epidermal junction
  - Compound – into dermis
  - Intradermal – dermis only
- Hemangioma
  - Common benign tumor of blood vessels
  - "strawberry hemangioma" occurs at birth, regresses within a year
- Keratoacanthoma
  - Rapidly growing crater-like mole
  - May represent a form of squamous cell carcinoma
- Seborrheic Keratosis
  - Common epidermal tumor
  - Trunk, head, neck
  - Flat, brown, velvety "stuck on" plaque
  - Sign of Leser-Trelat is paraneoplastic
- Actinic Keratosis
  - Epidermal dysplasia
  - Rough spots on sun-exposed skin
  - Some will become malignant (if untreated)
  - Treatment – freezing, curettage

Malignant Tumors

- Basal Cell Carcinoma
  - Malignant tumor of basal layer
  - Older patients, sun exposure
  - Pearly nodule, never metastasizes
- Squamous Cell Carcinoma
  - Malignant tumor of squamous epithelium
  - Older patients, sun exposure
  - Red nodule, can metastasize
- Melanoma
  - Malignant tumor of melanocytes
  - Dramatically increasing incidence
  - Sun exposure, can arise from benign nevus
  - Diagnostics
    - Asymmetry in shape/color
    - Border irregular
    - Color Change
    - Diameter >5mm
    - Elevation/textural change in lesion
  - Types of Melanoma
    - Superficial spreading
    - Nodular
    - Lentigo maligna
    - Acral lentiginous
  - Prognosis (directly related to invasion depth
    - <1mm – 80-95% 5 year survival
    - 1-2mm – 30-60% 5 year survival
    - 2-4mm – 35% 5 year survival
    - Presence of metastases important
  - Prevention
    - Avoid sun exposure
      - use sunscreen
      - protective clothing
    - Monthly skin self-exams
    - Physician screening of high risk patients
- Vascular Tumors
  - Kaposi Sarcoma
    - Malignant blood vessel tumor
    - Red skin bumps
    - Correlated with Ashkenazy Jews, AIDS patients
  - Angiosarcoma
    - Malignant blood vessel tumor
    - Very poor prognosis

Non-neoplastic Skin Pathology

Terminology

- Erythema – redness - Macule – flat lesion - Patch – large macule, <1cm - Papule – raised lesion	- Plaque – large papule, >1cm - Vesicle – blister - Bulla – large blister - Pustule – blister that contains pus

Infectious Disorders

- Impetigo
  - Affects kids
  - Crusty pustules on face – S.aureus, S.pyogenes
- Erysipelas
  - Face/scalp
  - Sharply circumscribed erythematous plaque – S.aureus, S.pyogenes
- Necrotizing Fasciiitis
  - Redness, pain, gangrene
  - Multipathogenic
  - Need early surgical intervention, IV antibiotics
- Acne
  - Clogging of sebaceous glands, bacterial inflammation of hair follicles/sebaceous glands
    Proprionibacterium acnes
  - Comedones (blackheads) and/or pustules
- Ringworm (Tinea)
  - Named after anatomic site (tinea pedis = athletes foot, corporis = body, capitis = head)
  - Red, inflamed, sometimes scaly round lesions
  - More common in children
- Sporotrichosis
  - Sporotrichum schenkii
  - “rose gardener’s disease”
  - Painless papule becomes open sore
- Verruca Vulgaris
  - Common wart, HPV correlated
- HSV
  - Type I – cold sores
  - Type II – genital herpes
- Molluscum Contagiosum
  - Pox virus, very contagious
  - Centrally-umbilicated red papules
- Erythema Multiforme
  - Correlated to HSV, sometimes drug related
  - “target” lesions/vesicles on skin, mucous membrane
  - Steven-Johnson syndrome – very rare, very severe skin necrosis
- Scabies
  - Sarcoptes scabei
  - Worldwide epidemic
  - Itchy scratch on hands/feet, abdomen/groin

Inflammatory Disorders

- Psoriasis
    - Common, chronic, inherited
    - Silvery scales over itchy red skin
    - Patients may also have arthritis of the hands
- Lichen Planus
    - Common, chronic, immune mediated
    - Purple polygonal papules on the skin
    - Lacy-appearing lesions (Wickham's striae), erosions, leukoplakia of mucosal membranes
- Atopic Eczema
    - Usually inherited
    - Itchy rash, history of atopic disease (asthma, hayfever)

Bullous Disorders

- Pemphigus Vulgaris
    - Antibodies against intercellular junctions (between squamous cells)
    - 40-50y/o adults
    - Mouth first, then skin
    - Superficial bullae that erupt easily
- Bullous Pemphigoid
    - Antibodies against basement membrane of epidermis
    - Elderly
    - Groin area, axilla, arms
    - Big subepidermal bullae