CELL INJURY AND REPAIR

NORMAL -vs- ABNORMAL CELLS:

- **Residual Bodies** lysoosomal waste vacuoles that are not excreted.
- **Lipofuscin** lysoosomal waste material having a brown appearance.

AMYLOID: Heterogenous collection of fibrillar protein. Amyloid can be differentiated from hyaline by its **Congo Red** stain. Amyloid will stain red with Congo Red and Hyaline won't.

APOPTOSIS: Programmed cell death that occurs normally in development. As opposed to Necrosis.

ATROPHY: Decrease in cell size and/or number.

- **OSTEOPOROSIS** = Atrophy of the bone matrix.

CALCIFICATION: Deposition of calcium salts in tissue

- **Dystrophic Calcification**: Abnormally necrotic tissue. Occurs in previously damaged tissue, with normal Ca$^{2+}$ levels.
- **Metastatic Calcification**: Calcification from hyperparathyroidism -----> hypercalcemia; or from renal failure.

NECROSIS: *Irreversible* cell death. Necrosis has occurred if the cell membrane and nucleus are destroyed.

- Types of Necrosis:
  - **Caseous Necrosis**: Necrosis that looks like cheese. Found in *tuberculosis* and some fungal diseases. It forms in response to intracellular pathogens such as *Mycobacteria*. It often is found in association with granulomas.
  - **Coagulation Necrosis**: Sudden cut off of blood supply to an organ, particularly heart or kidney. It leads to pyknosis, karyolysis, and karyorrhexis.
    - In kidney, you end up with a wedge-shaped contracted scar.
  - **Liquefaction Necrosis**: Transformation of solid tissue into fluid.

- Sign of Necrosis:
  - **KARYOLYSIS**: Irreversible cell death characterized by lysing of nucleus, due to action of DNAase and RNASE.
  - **KARYORRHEXIS**: Irreversible cell death characterized by fragmentation of the nucleus.
  - **PYKNOSIS**: Irreversible cell death characterized by condensation of the nucleus and clumping of chromatin.

DEATH: Cessation of normal body functions. Legally, brain-death, or loss of higher cortical function.

DYSPLASIA: Abnormal differentiation or maturation of tissue.

GANGRENE: Massive widespread ischemia.

- **WET GANGRENE**
- **DRY GANGRENE**: *Mummification* of tissue.
HEMOSIDERIN: Iron-containing pigment derived from hemoglobin.

- **Hemochromatosis, Hemosiderosis**: Accumulation of brown hemosiderin in liver.
  - **Primary Hemochromatosis**: Innate metabolic defect.
  - **Secondary Hemochromatosis**: Hemochromatosis secondary to Spherocytosis, Sickle Cell Anemia, or immune reaction to blood transfusion.
- Hemosiderin is a by product of hemolysis of blood.
- Hemosiderin is normally present, in small amounts, in some tissues.
- **Prussian Blue Reaction**: Hemosiderin will show up by the Prussian Blue Reaction, indicating the presence of iron inside granules.

HYALINE: **MALLORY'S HYALINE**: Keratin-like intracellular intermediate filaments that accumulate in liver with alcoholism. Eosinophilic.

HYDROPIC SWELLING: Reversible cell injury characterized by an influx of water and sodium chloride, and vacuolation of cytoplasm.

HYPERPLASIA: Enlargement of an organ due to increase in number of cells.

- Thyroid
- Prostate (Benign Prostatic Hyperplasia)
- Skin Warts, from **Human Papilloma Virus (HPV)**
- Childhood (not adult) obesity may play a role in hyperplasia.

HYPERTROPHY: Increase in size of an organ due to increased cell-size.

- **Left Ventricular Hypertrophy** from hypertension.
- **Right Ventricular Hypertrophy** originates from Left Ventricular Hypertrophy —> Pulmonary Hypertension (Cor Pulmonale) —> Right Ventricular Hypertrophy.

LIPOFUSCIN: Indigestible lysosomal waste-products, which accumulate in old-age. Pigment-like and rich in lipid.

LYSOSOMAL STORAGE DISEASES: Failure or incomplete digestion in lysosomes.

- **Von Gierke's Disease**: Glycogenosis.
- **Pompe's Disease**: Abnormal accumulation of Glycogen in lysosomes due to acid maltase deficiency.

METAPLASIA: Change from one cell type to another.

- Lung Metaplasia: **Simple Columnar** —> **Squamous**. Pre-cancerous.
- **Barrett Esophagus**: Stratified Squamous —> Intestinal
- **Myocytes**: Muscle —> Bone. Ossification.

PIGMENT: Any substance that has its own color. May be endogenous or exogenous.

- **Bilirubin**: Brown-red; heme-byproduct
- **Hemosiderin**: Brown' heme-byproduct
- **Lipofuscin**: Brown waste-product. Brown pigment in liver can by lipofuscin or hemosiderin.
- **Biliverdin**: Green; oxidized bilirubin.
- **Prussian Blue Test**: Test for the presence of heme. Brown pigment will turn to blue with this test if heme is present.

PROGERIA: Disease characterized by early onset of aging. Has a genetic origin.

WERNER'S SYNDROME: Another aging disease, where a 25-yo man looks 80. Tight puckered skin.

- Shows symptoms that are all related to aging: cataracts, deafness, diverticulitis, hypertension, osteoarthritis.
VACUOLAR DEGENERATION: Dilation of organelles \(\rightarrow\) accept fluid inside RER, maybe in mitochondria. Accumulation of lipid and glycogen.

**INFLAMMATION**

**ABSCESS:** Walled off, circumscribed cavity, filled with pus (Neutrophils).

Cardinal Signs of Inflammation:

- **Rubor:** Redness, from **hyperemia** (increased blood flow) and vasodilation.
- **Dolor:** Pain, from (1) swelling \(\rightarrow\) stretch sensory receptors, and (2) inflammatory mediators (bradykinins)
- **Calor:** Heat, *but only if the inflammation is in extremities*, because it comes from increased blood flow to the periphery.
- **Tumor:** Swelling, from (1) inflammatory edema, and (2) Triple Response of Lewis
- **Functio Laesa:** Loss of function, from reflexional disuse due to main, and mechanical / structural necrosis and/or healing.

**ACUTE PHASE RESPONSE:**

- **ACUTE PHASE (HEAT-SHOCK) PROTEINS:** Proteins produced early in inflammation, usually by hepatocytes.
  - **Interleukin-6** (IL-6): This cytokine will incite the production of these proteins.

**CORTICOSTEROIDS:** Cortisol. Antiinflammatory properties = inhibit Cyclooxygenase-2 and blocks phospholipases in target-cell membrane.

**MARGINATION:** Leukocytes moving from the center of a vessel toward the periphery, in order to effect the process of recruitment.

**ADHESION MOLECULES:** Molecules responsible for margination and diapadesis of granulocytes into the extracellular matrix at the site of injury. They are expressed by **inducible genes** during the amplification phase of inflammation.

- **ICAM-1:** Up regulated on endothelial cell surfaces, in response to cytokine mediators. Therefore important in the process of recruiting lymphocytes to inflammatory site.
- **INTEGRINS:** Vital to genesis of the cellular phase of the inflammatory response. It is instrumental to cell-cell and cell-matrix interactions among migrating cells.
  - In particular, they increase adherence of leukocytes to endothelial-cell lining during migration.
- **SELECTINS:** Lectin-like molecules that are important in the very initial reaction between leukocytes and endothelia -- in the process of margination.

**DIAPEDESIS:** Transmigration of leukocytes from the vasculature into the extracellular space. Involves adherence to endothelium, extension of pseudopodia between endothelial cells, and migration between endothelial cells.

**NITRIC OXIDE (EDRF, Endothelium-Derived Relaxin Factor):**

- It is **Inducible NO-Synthase** -- not Constitutive -- that is responsible for inflammatory vasodilation. Macrophages and Neutrophils will create lots of NO under the stimulation of the inducible form of the NOS gene.

**OPSONISATION:** Coating a bacterium or particle in order to facilitate its phagocytosis.
• **C3b** is an opsonin derived from the complement system.

• **Immunoglobulins** opsonise many bacteria, making them more easily phagocytosed, as Neutrophils have receptors for the Fc (common) region of the Ig molecule. This extra binding region facilitates higher affinity binding for the bacterium or foreign particle.

## EDEMA:

### Non-Inflammatory Edema:  Swelling by excessive hydrostatic pressure (hypertension) or loss of oncotic pressure (hypoalbuminemia, gloerulonephritis, kwashiorkor -----> ascites + peripheral edema).

  - Primarily serous **TRANSUDATE** (specific gravity < 1.015)
  - **NEPHROTIC SYNDROME**: Loss of albumin -----> proteinuria -----> hypoalbuminemia -----> non-inflammatory edema.

### INFLAMMATORY EDEMA:  Swelling, as an inflammatory response, resulting from cytokine-mediated increased vascular permeability, and anaphylaxis.

  - A dense **EXUDATE** of some sort can be recovered from the fluid. Specific gravity > 1.015
    - **Fibrinous**: Containing fibrin, of a fibrinous quality.
    - **Purulent**: Containing pus, i.e. neutrophils.
    - **Suppurative**: Containing large numbers of neutrophils, in conjunction with liquefactive necrosis.
    - **Sanguinous**: Containing erythrocytes
    - **Serous**: Of a watery quality, and containing few or no cells.

### POST-CAPILLARY VENULE:  These vessels are the primary targets for increased vascular permeability, via cytokines, by constricting endothelial cells.

## Process of Inflammation:

### INITIATION:  Ubiquitous proinflammatory enzymes are in the blood.

  - **Platelets** produce inflammatory mediators
    - **Thromboxane-A2 (TXA2)**: Cleaves Prothrombin -----> Thrombin to induce clot formation.
  - First **vasoconstriction** occurs, then vasodilation occurs later.

### AMPLIFICATION:  What happens after initiation of the inflammatory response. Characterized by:

  - General properties:
    - Local activation of precursors
    - Autocatalytic feedback loops: Kallikrein has positive feedback on the proteolytic activation of more Factor XII.
    - Expression of **inducible genes** for production of Cyclooxygenase-2
    - Upregulate expression of CAM molecules on the surface of tissue for recruitment of leucocytes to the area
    - **FAILSAFE MECHANISMS**: Two things are required for inducible genes to be induced. This helps to assure that the inflammatory mediators are not released until the cells have reached the site of injury.
      - Adhesion molecules must be present, an indication that the cells are out of the blood stream and have reached tissue-injury site.
      - Serum is require for some of the proenzyme. Serum is only present once a clot has already occured.

### TERMINATION

  - **INHIBITORY MEDIATORS**: **IL-10** and **TGF-beta** have inhibitory properties.
    - IL-4 and IL-5 also have antiinflammatory properties.
    - **Glucocorticoids** in circulation are anti-inflammatory. They act by inhibiting the expression of inducible genes.

## Different Forms of Inflammation: This is really a continuum.

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<thead>
<tr>
<th>Vascular Changes</th>
<th>ACUTE</th>
<th>CHRONIC</th>
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<tr>
<td>Vasodilation</td>
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<td>Minimal</td>
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### Cellular Infiltrates

**Increased permeability**

- Primarily neutrophils
- Mononuclear leukocytes, macrophages

### Stromal Changes

- Minimal
- Edema and separation of layers
- Fibrosis, cellular proliferation, scarring.

### Cell Infiltrates

- **Acute**: Common to find purulence (Neutrophils)
- **Subacute or Chronic-Active**: Intermediate between acute and chronic.
- **Chronic**: Find a lot of mononuclear leukocytes (macrophages), and associated with Granulomas.

### DISTRIBUTION

- **Focal**: Centered around a single source, such as a localized pathogen, local injury, or foreign body.
- **Multifocal**: Centered around multiple single sources.
  - **SECONDARY SYPHILLUS** presents with *multifocal* dermatitis.
- **Diffuse**:

### COMPLEMENT:

- **Classical Pathway**: Requires antibodies to activate.
  - Will produce anaphylatoxins C3a, C4a, C5a.
  - C4a is *only* produced by the classical pathway.
  - Leads to formation of the **MEMBRANE ATTACK COMPLEX**: C5b,6,7,8,9 form a lipid-soluble macroprotein that permeabilizes the bacterial membrane ------> rapid bacterial cell lysis.
- **Alternative Pathway**: Does not require antibody to activate.
  - Will produce anaphylatoxins C3a, C5a.
  - **Endotoxin** triggers the alternative pathway but not the classical pathway. Endotoxin is released by gram-negative bacteria.

### Anaphylatoxin:

- Examples of compounds:
  - **C3a**:
  - **C4a**:
  - **C5a**: *Very important inflammatory mediator*. The most important *initiator* of acute inflammatory response.
    - Anaphylactic Properties: Vasodilation and increased permeability.
    - Chemotactic Properties: Attract PMN's to the site of infection.
  - Effects:
    - Inducement of smooth muscle contraction.
    - Increased vascular permeability.
    - Degranulation of mast cells and basophils (IgE mediated)
  - **C3b**: An **Opsonin** that binds to bacteria, making them easier targets for phagocytosis by macrophages and neutrophils.

### HISTAMINE:

Vasoactive amine that increases vascular permeability. There are two histamine receptors.

- **H1-Receptor**: More important in the induction of increased vascular permeability, by inducing contraction of post-capillary venule endothelial cells.
- **H2-Receptor**: Found in stomach, and promotes secretion of acid in stomach.

### EICOSANOIDS:

Derivatives of **Arachidonic Acid**

- **PROSTANOIDs**: These metabolites are products of Cyclooxygenase.
  - **PROSTAGLANDINS**: Have a wide variety of pro-inflammatory effects. PGH₂ is the main one.
  - **THROMBOXANES**: TXA₂ is produced in quantity by platelets, and is vasoconstrictive and causes platelet aggregation. TXA₂ is derived from cyclooxygenase.
    - **SERUM**: Once you form an initial clot, that releases additional inflammatory mediators that further accelerate the process; sort of a positive feedback effect.
    - **EFFECTS**: Causes the formation of clots, and is a potent vasoconstrictor.
CYCLOOXYGENASE (PGH-SYNTHASE): Enzyme creates the prostanoids. It has two isoforms:
- **PGHS-1: Constitutive PGH-Synthase** is critical for low-level production of prostaglandins to maintain homeostasis, such as maintaining gastric lining.
- **PGHS-2: Inducible PGH-Synthase**: Found in high concentration in leucocytes, allowing them to produce large amounts of prostanooids at the site of infection, once initiation has occurred.
  - **Aspirin** irreversibly inhibits Cyclooxygenase-2 (PGH-2), this inhibiting production of prostaglandins (anti-inflammatory), and thromboxanes (anti-inflammatory, blood thinning).
  - **Indomethacin** is another drug with similar properties -- inhibit cyclooxygenase.

- **PROSTACYCLIN, PGI₂**: It is a powerful vasodilator; it antagonizes, inhibits, and opposes the effects of TXA₂. An overbalance of TXA₂ will result in platelet aggregation and inflammation.
  - It aids in the dissolution of clots by opposing the action of TXA₂.
- **HETE's**: Some of them are chemotactic for neutrophils and eosinophils.
- **LUEKOTRIENES**: Formed by Lipooxygenases, and having a wide range of pro-inflammatory properties.
  - Leukotrienes, LTB4, LTC4, LTD4, LTE4 are slow-reacting substances of anaphylaxis.
  - LTB4 is also a potent chemotactic factor for neutrophils.
  - These are important in Type-1 Hypersensitivity reactions.

**CYTOKINES**: Local factors having a variety of function, and released by Lymphocytes (Lymphokines), and Granulocytes (Interleukins).

- **Colony Stimulating Factors (CSF's)**: Have a growth effect on leucocytes. Released by macrophages and lymphocytes.
- **NETWORK**: Cytokines have overlapping, redundant effects, and generally a deficiency of one does not ruin the entire system.
- **INTERFERONS**:
  - **alpha,beta-INTERFERON (Type 1)**: Best known for antiviral properties. The alpha-beta receptor is ubiquitous on all cell types.
  - **gamma-INTERFERON (Type 2)**: Has a separate receptor, integral to the inflammatory response.
    - Promotes formation of giant cells in granulomatous infection.
    - **Interferon-gamma and ENDOTOXIN synergize** to make huge amounts of Inducible NO-Synthase ------> systemic anaphylaxis.

**HORMONES**:

- **AUTOCOIDS**: Hormones that act on the same cell from they are secreted. An example is **PGE₂**.
- **SEROTONIN**: Vasoactive amine, with vasodilatory effects, released by several cells, particular platelets.

**LYMPHOCYTES**: Are found prevalent in *chronic* inflammatory states.

- **B-CELLS**: They bear immunoglobulins on their surface.
  - **PLASMA CELLS**: Mature B-Cells, with clockface nucleus, that secrete IgG antibodies. Their presence is associated with chronic infection.
- **T-CELLS**:
  - **Lymphocytosis**: Increase in total number of lymphocytes.
  - **Lymphopenic**: Deficient in lymphocytes; lymphopenia.

**MONONUCLEAR LEUKOCYTE**: Macrophages and Monocytes.

- **Macrophages** have a wide variety of effects:
  - Antigen presentation to **T₃₉** cells.
  - Sacvenging and degradation of dead tissue and effete cells.
  - Activation of host defense against enemies.
  - Precursors to epithelioid and giant cells in granulomatous inflammation.
- **Monokine**: A cytokine produced by a monocyte.
OXYGEN-INDEPENDENT DEFENSES: Released by both PMN's and mononuclear leucocytes.

- **Bactericidal Permeability Increasing Protein (BPI):** Cationic protein. It strongly increases the permeability of bacterial cell walls.
  - It is contained in the primary granules of *Neutrophils*.
- **Major Basic Protein:** Found in the lysosomes of *Eosinophils*.
- **Defensins:** Found in the primary granules of *Neutrophils*. Defensins can kill fungi and viruses as well as bacteria.
- **Lactoferrin:** Chelate iron, to starve aerobic bacteria. Found in secondary granules in neutrophils.

GRANULOCYTES:

- **BASOPHIL:** Least common of the granulocytes. Horseshoe nucleus.
  - Similar in structure and function to Mast Cells, but having a different cell lineage.
  - Have lots of *IgE-Receptors* and thus partake in allergic response.
  - Release lots of vasoactive mediators: histamine, PAF, Leukotrienes
- **NEUTROPHIL:**
  - Morphology / Life-Cycle:
    - Tripartite nucleus. Also known as *Polymorphonuclear Leucocyte (PMN)*, because of the morphology of its nucleus.
    - Neutrophils are fully mature when released into circulation, but can be further stimulated by cytokines and growth factors at sites of inflammation.
    - Termed a professional phagocyte, for having extraordinary phagocytic properties.
  - LEFT SHIFT: Test; an increase in the number of immature neutrophils in circulation, indicating that the bone marrow is having trouble meeting the demand for neutrophils.
    - Degenerative Left Shift: A decrease in the absolute number of neutrophils; bad news.
    - Leukemoid Reaction: Change in the leukogram, which can immitate leukemia without actually being it.
  - Neutropenia: Deficiency of neutrophils.
  - Neutrophilia: An absolute increase in the number of neutrophils.
- **EOSINOPHIL:**
  - Also sometimes known as a PMN, because of the morphology of its nucleus.
  - Particularly present in (1) allergice reactions, and (2) parasitic infections.
  - Eosinophil Catioinic Protein: Unique basic protein that is toxic to certain parasites.
  - Eosinophilia: The condition of having an excess number of eosinophils in the blood.

KALLIKREIN-KININ SYSTEM: Activation system in acute inflammation leading to production of bradykinin.

- **Bradykinin:**
  - Potent vasodilator.
  - Potent smooth muscle contraction.
- **Kallikrein:** Has potential to cleave C5 -----> C5a, which is a potent chemotaxic agent.
- **Hageman Factor (Factor XII):**
  - It causes the conversion of Pre-Kallikrein to Kallikrein. (formation of bradykinin)
  - It causes the conversion of Plasminogen to Plasmin. (clot lysis)

CHEDIKA-HIGASHI SYNDROME: Inability to form phagolysosomes, due to inability for lysosomes to fuse with phagosomes inside phagocytic cells.

- Deficiency of *Cathepsin-G* in lysosomes.

CHEMOTACTIC FACTORS: Factors that induce chemotaxis. Chemotaxis is the process of a leucocyte sensing a minute difference in concentration gradient between the front and back of cell, and thereby directing its movement toward the source of the gradient.

- **SOURCES:**
  - *N-Formyl Peptides* in bacteria are chemotactic for neutrophils.
  - *C5a* is chemotactic for neutrophils.
- Eosinophil Chemotactic Factor (ECF) is chemotactic for eosinophils and is commonly found in anaphylactic allergic reactions.
- TGF-beta is chemotactic for fibroblasts and macrophages, and promotes collagen synthesis.
- Leukotriene-B4 (LTB4) is chemotactic.

**PRIMING** occurs as the leukocytes follow the chemotactic gradient. They are metabolically getting ready for the site of infection.

**EFFECTS of CHEMOTACTIC AGENTS:**
- They increase the number and affinity of Fc receptors on neutrophils, and move them to the front of the cell, in order to promote Ab-dependent opsonisation.
- They mobilize granules to the front of the cell.
- Enhanced motility
- Enhanced oxidative metabolism (priming)
- Expression of inducible genes
- Increased phagocytosis mediators
- Indirect proinflammatory mediators.

**RECRUITMENT:** During this process we develop turbulent blood flow and have **hemoconcentration** as cells migrate to the area.

**GRANULOMATOUS INFLAMMATION:** Chronic inflammation, occurring after the acute-phase response.

**EPITHELIOID CELL:** Derived from macrophages, uniquely found in chronic granulomatous inflammation. All granulomas have epithelioid cells.

**GIANT CELL:** Commonly found in granulomas, but not required. They are derived from the fusion (syncitium) of several macrophages.
- Interferon-gamma and Interleukin-4 (IL-4): Both of these cytokines promote the formation of giant cells from macrophages. These cytokines are produced at the site of the lesion.
- FOREIGN BODY GIANT CELL: Giant cell containing foreign particles, often visible.
- LANGHANS GIANT CELL: Giant cell having characteristic horseshoe configuration of its multiple nuclei.

- Two-types of Granulomas:
  - FOREIGN-BODY GRANULOMA: Granulomas formed in response to indigestable materials.
  - ALLERGIC (IMMUNE) GRANULOMA: Formed in Type-IV Delayed hypersensitivity reactions.

**CHRONIC GRANULOMATOUS DISEASE:** Deficiency of NADPH-Oxidase -----> leucocyte cannot create superoxide anion and thus cannot kill bacteria. Bacteria are phagocytosed but not killed.
- Failure to kill these bacteria leads to chronic, and finally, granulomatous inflammation.
- SARCOIDOSIS: Chronic granulomatous disease, of unknown cause, characterized by non-caseating granulomas, i.e. granulomas without a center of caseous necrosis.

**GRANULOMA STRUCTURE:**
- CENTER: Caseous Necrosis center, in the case of a Caseating Granuloma, as in Tuberculosis.
- INNER LAYER: Epithelioid Cells + Multinucleated Giant Cells -- specialized macrophages.
- MIDDLE LATER: Lymphocytes are found next, in immune granulomas.
- OUTER LAYER: Predominantly fibroblasts.

**GRANULATION TISSUE:** Tissue that is in the process of healing, and having nothing to do with an inflammatory granuloma or granulomatous infection.

**HAGEMAN / FIBRINOLYTIC SYSTEM:** Activating system for amplifying the inflammatory response. **Hageman Factor** (XII) creates fibrin from fibrinogen, which yields plasmin to break down fibrin to fibrin-split products, which have inflammatory properties and are diagnostic of inflammatory infections.

- Elevated Fibrinogen levels indicate that an infection is present.
- You can also measure that Erythrocyte Sedimentation Rate (ESR) as a non-specific indicator of infection.

**PLATELETS:** The most ubiquitous source of proinflammatory mediators.

- In particular, they are a source of Vasoconstrictive, clot-forming **Thromboxane A2 (TxA2)**.
PLATELET ACTIVATING FACTOR (PAF): Lipid, not stored in granules; extremely vasoactive inflammatory intermediate.

- It is mobilized from the cell membrane of many different cells, and produced by the action of **Phospholipase A₂**.
- **EFFECTS:**
  - Activates platelets to synthesize TXA₂ (hence the name!)
  - Causes strong vascular smooth muscle contraction and increased permeability via inducing synthesis of Inducible NO-Synthase in vascular endothelium.
  - Strongly chemotactic.
  - Causes leukocyte aggregation, adhesion, and priming -- i.e. it stimulates them to synthesize oxygenated intermediates.
- **PAF is 100x to 1000x more potent than Histamine in its vasoactivity.**

CONSOLIDATION: Especially in lung, conversion of an inflamed tissue into a dense and firm tissue.

- **Gray Hepatization:** Late consolidation of the lung, developing firmness. The inflammatory process has continued long enough for hyperemia to subside, leaving primarily leukocytes.
- **Red Hepatization:** Early consolidation, characterized by firmness and redness from hyperemia. Inflammatory process is in acute phase.

OXYGEN-DEPENDENT BACTERIOCIDES: Reactions involving oxidative radicals and requiring oxidative metabolism.

- **Antioxidants** inhibit the formation of oxidative radicals, or aid in breaking them down.
  - **Glutathione Peroxidase**
  - Vitamin-E
  - Superoxide Dismutase
  - Catalase

FRUSTRATED PHAGOCYTOSIS: Occurs when leukocytes cannot completely engulf a cell because the cell is too large. So, instead they exocytose their digestive enzymes to the surrounding tissue, resulting in **autoinflammatory tissue injury**.

PRURITUS: Itching; non-inflammatory. Note spelling.

PYROGEN: Fever-forming. Endogenous pyrogens include:

- Interleukin 1 (IL-1)
- Tumor Necrosis Factor, TNF-alpha

REPAIR, REGENERATION AND FIBROSIS

CELL TYPES and Regenerative Ability:

- **LABILE CELLS:** Cells with a short lifespan that constantly proliferate: skin, gut, hematopoetic cells.
- **PERMANENT CELLS:** Cells that cannot regenerate once they are destroyed. A destroyed cell will form a scar. **Brain, Heart.**
- **STABLE CELLS:** Cells that are in G₀ of the cell-cycle and don't normally divide, but can be induced to divide quickly upon injury. These cells have good regenerative capacity. **Liver, Renal proximal convoluted tubule.**
  - **ACUTE TUBULAR NECROSIS** occurs with O₂-deprivation in O₂-hungry renal tubules. *As long as the basement membrane is intact*, the tubule cells will regenerate.
    - **Oliguric Phase:** Little urine output during necrosis -- kidney shuts down.
    - **Polyuric Phase:** Lots of output during healing process. Kidney functions but the proximal tubules are busy regenerating, thus reabsorption is very low.
Surgical Wounds:

- **PRIMARY INTENTION**: Letting a surgical wound heal without a big scar, where the wound has neatly apposed edges.
- **SECONDARY INTENTION**: Letting a surgical wound heal and leave a big scar, called granulating in from the bottom up, with edges that are not neatly apposed.
  - This is necessary in appendectomies and abdominal surgeries in general, in order to assure that the wound doesn't later burst open.

**PYELONEPHRITIS**: Pus in the collecting tubules. You get a **urine cast** of PMN's resembling the shape of the tubules.

- If you only partially treat it, you can get chronic pyelonephritis as a result.

**EXTRACELLULAR MATRIX**: The materials over which cells migrate and travel during development and wound-healing. It contains five primary parts

- **COLLAGEN**: There are four types of Collagen we need to know. Collagen is synthesized and secreted by fibroblasts.
  - **TYPE I COLLAGEN**: Skin, bone, and tendon.
  - **TYPE II COLLAGEN**: Cartilage.
  - **TYPE III COLLAGEN**: Aorta, uterus, and GI smooth muscle. Reticular collagen.
  - **TYPE IV COLLAGEN**: Basement membranes, exclusively.
  - **Scleroderma** is proliferation of collagen.
- **BASEMENT MEMBRANE**: Made of Type IV Collagen.
  - Synthesized by basal cells of epithelia.
  - FNXXN: Filtration in the kidney. Basement membrane contains **heparin sulfate**, which is negatively charged, to guide filtration and keep out big negatively charged proteins like albumin.
- **FIBRONECTIN**: It has several specific binding sites, and generally functions as a guide, to allow cells to migrate through the matrix.
  - Binding sites:
    - Collagen binding site
    - Fibrinogen binding site
    - Proteoglycan binding sites
    - Binding sites for various bacteria.
  - Wound Healing: Fibronecin plays an important cross-linking function.
- **ELASTIC FIBERS**: Pliable structures like arteries and uterus.
  - Similar to collagen (containing Pro and Lys), but contains almost no hydroxyylated structures.
  - **Marfan Syndrome** is a defect in elastic fibers.
- **PROTEOGLYCANS**:

**INTEGRINS**: Transmembrane proteins that interact with the ECM. They may act as a communication link between intracellular environment and extracellular matrix. Via integrins, the ECM can modify cell behavior.

**CYTOKINES**:

- **MDGF, MACROPHAGE-DERIVED GROWTH FACTOR**:
- **PDGF, PLATELET-DERIVED GROWTH FACTOR**: Secreted by platelets, induces proliferation of fibroblasts, microglia, and smooth muscle.
  - May also serve as a chemotactic agent for inflammatory cells.
- **EGF, EPIDERMAL GROWTH FACTOR**: Induces proliferation of epithelia; essential for wound-healing.
  - Most cells have EGF-receptors. A kinase is activated as secondary messenger once EGF binds.
  - EGF also has pre-cancerous properties, if the EGF-receptor pathway is unregulated.
- **FGF, FIBROBLAST GROWTH FACTOR**: Promotes the growth of fibroblasts, endothelial cells, and smooth muscle.
  - It is also probably present in the process of angiogenesis.
- **TGF, TRANSFORMING GROWTH FACTOR beta**:
ANGIOGENESIS: Formation of new vasculature following injury. Occurs during formation of granulation tissue. FGF is a cytokine that is thought to induce angiogenesis.

- **Bartonellosis** and **Bacillary Angiomatosis** are two infectious processes that involve angiogenesis.
- Angiogenesis also occurs during some cancerous processes.

GRANULATION TISSUE: The initial response to a wound, early part of scar formation. Proliferation of fibroblasts and blood vessels. It may or may not include inflammatory cells.

- **CALLUS**: A type of granulation tissue that consists of bone or cartilage.
- **KELOID**: Hypertrophic or exuberant scar, often occurring in black people. If you excise a keloid, it will grow back.
  - Normal scar mature from Type-III (early) to Type-I (mature) collagen. Keloids remain as immature Type-III collagen.
- **CICATRIX**: Scar. Lots of fibroblasts, some with nucleoli (metabolically active). A little hemosiderin pigment is present.

HEALING: A response to tissue injury, and attempt to maintain homeostasis.

- **CONTRACTURE**: Exuberant, overactive contractile stage of wound-healing. This can result in a deformed scar.
  - **Dupuytren's Contracture** is idiopathic contracture of the palmar aponeurosis.
- **DEHISCENCE**: The bursting of a wound. Failure of tensile strength of scar.
  - Abdominal wounds are the most subject to dehiscence, thus surgeons let abdominal wounds heal by secondary intent.
  - Abdominal dehiscence can be provoked by coughing, vomiting, wound infection, or poor nutrition during the healing period.
- **THREE STAGES** to wound healing:
  - **INITIAL RESPONSE**: Initial cellular response to injury
    - **Neutrophils**: They are the first line of defense. They are chemotactically attracted to injury site by tissue factors. They arrive within hours.
    - **Macrophages** engulf the neutrophil debris, within days.
    - **Fibroblasts** finally arrive to begin the process of repair.
  - **CONTRACTION**: Bring the wound edges closer together.
    - **Myofibroblasts**: Looks like fibroblast but has contractile elements. Works in contraction of wound.
  - **REPAIR**: Secrete extracellular matrix (fibroblasts) and lay down a scar.
    - **Proteoglycans** are the first substances to be laid down, followed by formation of collagen.
  - **REGENERATION**: Regenerate epithelial tissues.
    - It occurs in liver and skin, as long as basement membranes are still intact. If basement membranes are gone, then a scar (in the case of skin) or micronodules (in the case of liver) will form instead.
- Factor that influence wound-healing:
  - **Overall Nutrition**: Proteins deficiencies and vitamin deficiencies (esp. Scurvy since Vit-C is required for collagen formation)
  - **Obesity** -----> poor vascularity -----> poor wound healing.
  - **Age**
  - **Race**: Blacks at higher risk of forming keloids.
- Complication in wound healing:
  - **Dehiscence**, or ulceration of the scar.
    - Infection, malnutrition, and hypoxia (poor vascularity) all increase the risk of dehiscence.

CIRRHOSIS: Result of a chronically damaged liver. Histologically it a combination of regenerated liver cells interspersed with fibrosis.

- **MICRONODULAR CIRRHOSIS**: **Alcoholic Cirrhosis**. Alcohol kills liver cells globally and destroys basement membranes. With BM's destroyed, when the liver tries to regenerate, it has no scaffolding on which to grow, and the result is formation of a bunch of micronodules, instead of uniform liver tissue.
Fibrosis runs from Portal Triad to Portal Triad, and works its way inward.

- **HEPATOMA**: Hepatocellular Carcinoma. Liver tumor occurs more prevalently in cirrhotic livers. Why?
  - Because the hepatocytes are constantly proliferating, thus increasing likelihood of malignancy.
  - Concurrent infection with Hepatitis-B or C in alcoholism is extremely common.
- **MACRONODULAR CIRRHOSIS**: Chronic Active Hepatitis. Nodules form similar to micronodular cirrhosis, except that injury spreads outward from focal points in the liver -- i.e. from points of viral infection. The response to this focal injury is formation of nodules which appear as macronodules.
- **FATTY LIVER**: Reversible damage due to alcohol.
  - Alcoholic hyaline is visible with fatty liver.

**CARDIAC DISEASE**:

- **CARDIAC TAMPONADE**: Blood in the pericardial sac, which can happen after an MI, at the time of maximal healing during formation of a scar in the myocardial muscle. Rare and instantly fatal.
  - Can happen about six days post-MI, during the late phase of healing when Macrophages are cleaning up debris.
  - The ventricular septum can also burst, leading to hypoxia and shock.
- **Reperfusion Injury** by oxidative radicals is a risk after 4 hours post-MI.

**IMMUNOPATHOLOGY**

**HYPERSENSITIVITY**:

- **TYPE-I: IMMEDIATE**. Mediated by IgE molecules binding to Fc-receptors on Mast Cells and Basophils.
  - Examples:
    - Hay Fever, allergic rhinitis, penicillin anaphylaxis.
  - SENSITIZATION: Initial formation of the IgE. Prior exposure to the allergen is required for an allergic reaction to happen later.
  - ANAPHYLAXIS: Anaphylaxis can occur by two separate processes -- either Mast Cell degranulation or complement-derived Anaphylatoxins. The result is the same but the mechanisms are different.
    - **MAST-CELL DEGRANULATION** occurs in an allergic response in results in release of the following:
      - **Histamine** has several effects:
        - Intense bronchial smooth muscle contraction
        - Increased vascular permeability
        - Increased secretion by nasal, bronchial, and gastric glands.
      - Proteases, Heparin
      - **Eosinophil and Neutrophil Chemotactic Factors (ECF, NCF)**: Eosinophilia is a common sign of a Type-I allergic reaction.
      - Membrane Derived Metabolites: **PGD2, LTB4, PAF** are also released in Mast Cell activation, although they weren't in granules. Prostaglandins and Leukotrienes are derived from Arachidonic acid, and PAF is not. All of them cause bronchospasm and increased vascular permeability.

- **TYPE-II: ANTIBODY-DEPENDENT CYTOTOXIC**. A reaction of soluble IgG, IgM antibody with membrane-bound antigen (usually autoantigen)
  - **COMPLEMENT**: IgG and IgM and activate Complement via Fc receptors on endothelial cells. Complement is then activated via Classical (antibody-dependent) pathway. Complement effects:
    - **Cell Lysis** through MAC. This accounts for hemolysis in certain kinds of hemolytic anemias.
    - **OPSONIZATION** via C3b which acts as an opsonin: phagocytic cells express **C3b-receptors** and can thus bind to targets. This also occurs in certain autoimmune hemolytic anemias.
  - **Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)**: Natural Killer Cells, as well as macrophages and some PMN's have Fc-receptors and can thus attack IgG-coated target cells and lyse them. This process occurs without phagocytosis.
    - This may play a role in Hashimoto's Thyroiditis.
• **TYPE-III: IMMUNE-COMPLEX.** Accumulation of immune-complexes, formed by soluble antibody and soluble antigen.
  - **SERUM SICKNESS:** Horse or bovine serum can be injected into human's as an antidote to bee venom or snake bites. The foreign serum will then induce formation of immune-complexes, which elicit symptoms 6 to 8 days later.
    - **SYMPTOMS:** Fever, arthralgia, vasculitis, acute glomerulonephritis.
  - **ARTHUS REACTION:** Experimental *vasculitis*, in which a localized injury is produced by immune complexes. Immune-complexes accumulate on vessel walls which activated complement -----> vascular endothelial lesions.
    - Fibrin will accumulate in vessel-walls which will result in a *fibrinoid necrosis* in the area.
      - Fibrinoid Necrosis of vascular walls is common in all Type-III diseases.
  - **PPD TB SKIN TEST** is also an example of a delayed hypersensitivity reaction.

• **TYPE-IV: DELAYED.** Antibody-independent, cell-mediated response of \(T_C\) cells against antigen. Reaction is generally 24 to 72 hours after allergen exposure.
  - **T-CELL Mediation:** T-Cells recognize the antigen directly and release *lymphokines* in response to it.
    - Immature CD4 cells mature and proliferate in response to antigen presented by macrophages or B-Cells. Mature \(T_H\) cells then release cytokines:
      - IL-2 stimulates growth of more \(T_H\) cells in an autocrine fashion.
      - IFN-gamma powerfully activates *Macrophages*, which can then further go onto activate fibroblasts via *TGF-beta*.
    - Cytotoxic Cells recognize antigens directly, and proliferate in response to it.
    - Natural Killer (NK) cells can also proliferate in Type-IV responses. They have Fc receptors and respond primarily to membrane glycoproteins, virus-infected cells, or tumor cells.
  - Type-IV (Cell-Mediated) defense is very important in battling against intracellular parasites such as *mycobacteria* (*tuberculosis*), and it often results in the formation of granulomas, as the activated Macrophages form Epithelioid cells.

THEORIES OF AUTOIMMUNITY: Autoimmune diseases have multiple etiologies.

- Abnormal T-Cell Function; lack of *supressor T-Cells*. This theory has the most evidence supporting it.
- Polyclonal B-Cell Activation
- Biological Mimicry, as in *Rheumatic Heart Diseases*, in which antibodies against streptococcal antigens cross-react with myocardium.

HYPERSENSITIVITY / AUTOIMMUNE DISEASES: Most auto-immune diseases, for unknown reasons, occur predominantly in woman, sometimes by a margin of 10:1 or greater.

- **ASTHMA:** Can be caused by a Type-I Hypersensitivity to exogenous allergens in the respiratory tract.
  - CHARCOT-LEYDEN CRYSTALS: Eosinophilic granules found in the mucus; diagnostic of asthma.
- **HASHIMOTO'S THYROIDITIS:** A combination of Type-II (organ-specific) and Type-IV (cell-mediated) auto-immune disease.
  - PATHOGENESIS: Type-II ADCC against thyroglobulin, and against thyroid peroxidase (microsomal bodies).
  - SYMPTOMS: Goiter, due to inflammatory infiltrates in the thyroid.
  - HASHITOXICOSIS: Severe hyperthyroidism, found in this disease.
  - OTHER DISEASES: Many other autoimmune diseases are commonly associated with Thyroiditis: SLE, Rheumatoid Arthritis, Sjogrens, Addison's, IDDM.
- **GRAVE'S DISEASE:** Type-II autoimmune attack against TSH-receptors in the thyroid gland, resulting in overactivation of them -----> Hyperthyroidism.
  - This is a disease where an auto-antibody acts as an *Agonist*.
- **MYASTHENIA GRAVIS:** Type-II autoimmune attack against Nicotinic Acetylcholine receptors -----> block Ach-receptors -----> Fatigueable Weakness.
  - This is a disease where an auto-antibody acts as an *Antagonist*.
- **GOODPASTURE'S SYNDROME:** Type-II Autoimmune attack against Collagen-IV basement membrane components.
SYMPTOMS: In Goodpasture's, the auto-antibodies attack primarily the Glomerular Basement Membrane and Pulmonary basement membrane -----> Renal Failure (Glomerulonephritis) and Pulmonary disfunction.
   - Classic dual symptoms are therefore hemoptysis and renal failure.
SYMPTOMS: Immunofluorescence shows a linear array of immunofluorescence, as antibodies bind to basement membrane.

- SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): Type-III Hypersensitivity in which immune complexes are formed against nuclear components in any lysed cells. This is the most common systemic auto-immune disease.
  - Anti-Nuclear Antibodies, ANA, Anti-dsDNA are the most common autoantibodies, but there are others.
  - SYMPTOMS:
    - Butterfly Malar Rash is very common.
    - Vasculitis
    - Glomerulonephritis
    - Polyarthralgia is the most common complaint. Synovitis also occurs.
    - Heart-problems can occur but are less common: Pericarditis, and non-bacterial vegetations on valve leaflets called Libbman-Saks Endocarditis.
    - SUN EXPOSURE makes the symptoms worse, as DNA is exposed to antibodies in the bloodstream.
  - DIAGNOSIS:
    - BAND-TEST: Look for immunofluorescence at the dermal-epidermal junction upon skin biopsy.
    - Immunofluorescence of Anti-dsDNA Antibodies is diagnostic of SLE.
    - Labs: Hemolytic anemia, thrombocytopenia (low platelet count), leukopenia.

- PEMPHIGUS VULGARIS: Large, easily erupted bullae on mucous membranes.
  - DIAGNOSIS:
    - Immunofluorescence shows a netline pattern of autoantibodies. Compare to Goodpasture's, which is linear.
    - Take a skin biopsy and look for antibodies (IgG), but it must be from a newly evolved lesion, otherwise it could be explained by infection.
    - Progressive denudation of skin will lead to infections.
    - They are very similar to burn patients in their needs and risks.

- SJOGREN SYNDROME: Also predominantly Type-III Autoimmune disorder characterized by sicca (dry eyes) and xerostomia (dry mouth). Second most common connective tissue disorder, after SLE.
  - Rheumatoid Factor is commonly found, whether or not they have Rhrumatoid Arthritis.
  - Associated with a 4-fold increased risk for malignant lymphoma.
- SCLERODERMA: Connective Tissue autoimmune disease characterized by excessive collagen deposition in skin and internal organs.
  - Etiology is associated with chromosomal abnormalities (breaks, translocations).
  - Most organ systems are involved, with generalized collagen deposition and scleritis found throughout.
  - SYMPTOMS:
    - Raynaud's phenomenon is often found early on.
    - Exertional dyspnea is found due to pulmonary interstitial fibrosis.
    - Polyarthritis.

- POLYMYOSITIS / DERMATOMYOSITIS: Autoimmunity against skeletal muscle and skin. In men, it is often associated with an underlying visceral cancer.
- WEGENER'S GRANULOMATOUS VASCULITIS: Small-vessel vasculitis; common to also find glomerulonephritis. Probably Type-IV reaction.
  - Saddle-shaped nose, with damage to the nasal septum.
  - Lung granulomas.
- RHEUMATOID ARTHRITIS: Antibody against the Fc portion of IgG, forming an immune complex which is then termed Rheumatoid Factor.
- CONTACT DERMATITIS: Type-IV delayed hypersensitivity. Poison Ivy.

IMMUNE DEFICIENCY DISEASES: Most congenial immunodeficiency diseases are X-linked and thus occur only in males.

- CONGENITAL X-LINKED HYPOGAMMAGLOBULINEMIA (XLA) (BRUTON'S DISEASE): Caused by a defect in the early-mature B-Cells. Pre-B Cells are detected but cannot mature.
  - Age: Infantile
• **COMMON VARIABLE IMMUNODEFICIENCY**: Hypogammaglobulinemia (deficient IgG). Pt presents with pyogenic infection.
  o **Age**: Adult, 30 years.
• **SELECTIVE IGA DEFICIENCY**: Most common of immunodeficiencies. B-Cell count is normal, but IgA is not synthesized or secreted. Could be a problem with class-switching or with the secretory pathway.
  o **Symptoms**: Recurrent or opportunistic GI-tract and respiratory infections.
• **DIGEORGE SYNDROME**: Congenital malformation of 3rd and 4th Brachial Pouches, resulting in no formation of Thymus.
  o **Patient** will present with severe **hypocalcemia** due to hypoparathyroidism (Parathyroid does not form normally).
• **SEVERE COMBINED IMMUNODEFICIENCY (SCID)**: Absence of both T and B-Cells. Onset at 6 months.
  o **Adenosine Deaminase Deficiency** is usually the cause in autosomal-recessive SCID (there is also an X-linked form). Deficiency of ADA leads to accumulation of deoxyadenosine and its derivatives (e.g., deoxy-ATP), which are toxic to immature lymphocytes.
• **CHRONIC MUCOCUTANEOUS CANDIDIASIS**: Specific immunodeficiency against Candida fungi and nothing else. Strange...
• **WISCOTT-ALDRICH SYNDROME**: Rare X-linked, cause unknown. It is a complete failure to produce antibodies against polysaccharides.
• **ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)**: Infection of CD4 cells by HIV retrovirus.
  o **Common Complications**: Opportunistic infections. Of course this list is not complete.
    ▪ **Persistent Generalized Lymphadenopathy**: Common early symptom. Persistent enlargement of lymph nodes with no apparent cause.
    ▪ **Kaposi Sarcoma** is a common skin cancer that occurs all over the body in AIDS and rapidly metastasizes.
    ▪ **Pneumocystis Carinii** is an opportunistic pathogen that frequently causes pneumonia in immunocompromised patients.
    ▪ **Cytomegalovirus**
    ▪ **Toxoplasmosis** occurs in the brain where it forms lesions that are evident on MRI. Toxoplasmosis occurs in normal people, too, but it doesn't form the lesion because our immunity can quickly wipe it out.
    ▪ **Candida** infections.
  o **gp120** is the name of the viral-coat protein, which recognizes CD4 receptors on T_H cells in order to gain entry into the cells.

**AGGREGATE**: Association of a peptide epitope with Type-I MHC complex. It can then react with CD8 cytotoxic cells.

**ENVIRONMENTAL PATHOLOGY**

**RADIATION**:

• **MECHANISMS OF INJURY**:
  o **DIRECT INJURY**: Radiation directly producing single or double-stranded chromosomal breaks in DNA.
  o **INDIRECT INJURY**: Ionizing radiation -----> radiolysis of water -----> **free oxygen radicals** -----> interact with DNA to produce mutations.
• **EFFECTS**
  o **LATE EFFECTS OF RADIATION**:
    ▪ Small arterial thickening (hyaline, collagenous), which may result in local ischemia.
    ▪ Mutation to fetuses exposed in utero
    ▪ Bone marrow hypoplasia
    ▪ Radiation dermatitis
    ▪ Radiation pneumonitis
    ▪ Induction of cancer:
      ▪ Leukemias and lymphomas
      ▪ Breast cancer
      ▪ Thyroid
      ▪ Lung
      ▪ Osteosarcoma
WHOLE BODY ACUTE RADIATION SYNDROME: Consisting of three distinct sub-syndromes

- HEMATOPOIETIC: 300 rads, pancytopenia develops after two weeks
  - Anemia, bleeding, infection
- GI: 1000 rads, destruction of GI epithelium
  - Diarrhea, dehydration, enteric sepsis
- CNS: 2000 rads, damage and death secondary to endothelial injury and cerebral edema.

TYPES OF RADIATION:

- ELECTROMAGNETIC (IONIZING) RADIATION: X-Rays and Gamma Rays
  - Produce ionization with subsequent free radical formation, damaging tissues.
- PARTICULATE RADIATION: Neutrons and charged particles (alpha, beta, protons, deuterons)
- ULTRAVIOLET:
  - Effects: Sunburn, photosensitivity reactions, cataracts, skin neoplasia.

MEASURES OF RADIATION:

- Rad (r): Radiant energy, expressed in ergs, that is absorbed by a tissue.
  - The absorption of radiant energy is biologically more important than the total amount emitted.
- Gray: 100 rads
- Relative Biological Effectiveness (RBE): Term comparing the effectiveness of different forms of radiation in producing the same effect.
- Roentgen (R): Measure of emission of radiant energy (not absorption).
- Roentgen-equivalent Man (rem): Describes the biological effects produces by 1 rad of high-energy biological radiation.

RADIOSENSITIVITY: Some cell-types (and tumors) are more radiosensitive than others

- HIGH SENSITIVITY: Cells that tend to divide a lot
  - Lymphomas
  - Gonads / Seminoma
- LOW SENSITIVITY: Cells that normally do not divide a lot
  - Osteosarcomas
  - Gliomas

RADIATION PNEUMONITIS:

- Often a side-effect of chemotherapy for lung cancer.
- There must be sufficient oxygen tension in the lung for it to occur. It won't occur in a COPD lung due to poor oxygenation.
- MORPHOLOGY:
  - intra-alveolar hyaline membranes
  - Interstitial edema and chronic inflammation
  - Infiltration and proliferation of mononuclears and fibroblasts, many with large atypical nuclei.

TYPES OF INJURY:

- ABRASION: Defect in skin caused by direct or tangential impact. Crushes or scrapes the epithelial surface.
- AVULSION: Tearing away of skin and underlying tissue.
- CONTUSION (BRUISE): Localized area of mechanical injury with focal hemorrhage.
  - HEMATOMA: Discrete hemorrhage within tissue, caused by mechanical injury.
- INCISION: Opening of skin by a cutting instrument, leaving apposed edges as in surgeon's knife.
- LACERATION: Discontinuity of the skin resulting from a tangential impact that splits and tears the epithelium.
- PUNCTURE WOUND: Injury made by a pointed instrument.
- CRUSH SYNDROME: Secondary body changes from muscle injury.
  - Muscle releases hemoglobin and myoglobin.
  - Hemoglobin in kidneys causes vasoconstrictive renal ischemia.
- ELECTRICAL INJURY:
  - Effects:
    - Causes burn to skin due to high electrical resistance of skin.
    - Disruption of neural conductance can cause cardiac arrhythmias.
- BATTERED CHILD SYNDROME:
  - Discrepancy between history and physical findings.
  - Wounds or injuries in different stages of healing.
- BLAST INJURY: Positive pressure from one direction followed by sudden negative pressure from the other direction.
• Results:
  - Thoracic collapse.
  - Multiple pulmonary hemorrhages
• IMMERSION BLAST: Positive pressure from all directions followed by sudden negative pressure.
  - Diaphragmatic lacerations
  - Visceral rupture

• FRACTURE:
  - Simple: Closed fracture
  - Comminuted: Bone is splintered or crushed.
  - Impacted: One bone fragment is firmly driven into another.
  - Incomplete: Continuity of the bone is not entirely destroyed.
  - Greenstick: One side of bone is broken while the other side is bent.
  - Stress: Fine hairline fracture without soft tissue injury.
  - Compound: Open fracture, open skin.
  - Pathologic: Due to weakening of bone by some pathologic process
    - Osteoporosis
    - Osteomalacia
    - Neoplasia
    - Osteomyelitis
• GUNSHOT WOUND: The hole of entrance is usually smaller than the hole of exit.
  - CONTACT WOUND: The only case where the hole of entrance is actually larger than the hole of exit.
    - Contact Ring: Abrasive collar around entrance wound from the gunpowder.
  - CLOSE RANGE
    - CLOSE-RANGE (< 1 ft):
      - Fouling: Grey-black discoloration, caused by heat, smoke, and small grains of burning powder.
      - Stippling: Marks produced by discrete larger particles of unburned powder.
    - CLOSE-RANGE (1-3 ft):
      - Stippling only -- no fouling.
    - CLOSE-RANGE (> 3 ft):
      - No fouling or stippling.
  - HOLE OF EXIT: Irregularly lacerated edges with no fouling or stippling.

• SOUND WAVE INJURY: To hair cells and other auditory components.

THERMAL INJURIES:

• BURNS
  - Degrees
    - FIRST DEGREE: Involving superficial epidermis only.
    - SECOND DEGREE: Deep partial thickness, involving epidermis with some viable dermal appendages capable of regeneration.
    - THIRD DEGREE: Full Thickness, both epidermis and dermis, and requiring grafts to heal.
  - Primary Effects: Necrosis, inflammation, fluid loss.
  - Secondary Effects:
    - Superinfection: Staph Aureus + Pseudomonas aeruginosa -- most frequent cause of death from burns.
    - Shock
    - Acute gastro-duodenal stress ulcer
  - INHALATION BURN: Respiratory hyperthermic injury.
    - Results:
      - Laryngeal and pulmonary edema
      - Adult Respiratory Distress Syndrome (ARDS)
  - ADULT RESPIRATORY DISTRESS SYNDROME (ARDS): Hyaline Membranes
    - Causes:
      - Trauma
      - Infection
      - Aspiration
      - Drugs: heroin, oxygen
      - Radiation
• **GENERALIZED HYPOTHERMIA**: Decrease in body temp. below 35°C (95°F). Results:
  - Cooling of blood perfusing the brain.
  - Increased vagal discharge leading to cardiac arrhythmias.

• **FROSTBITE**: Local freezing hypothermic injury with necrosis due to crystallization of water, vasoconstriction, endothelial damage, and thrombosis.

• **TRENCHFOOT**: Non-freezing hypothermic injury to feet. No water-crystallization.
  - Necrosis due to vasoconstriction, endothelial damage, and thrombosis.

• **HEAT STROKE**: Systemic hyperthermia.
  - **Classic Heatstroke**: Very young or elderly, and chronically ill, caused by drugs affected thermoregulation.
  - **Exertional Heatstroke**: Healthy adults, during vigorous exercise.
  - Effects: Hot dry skin, rhabdomyolysis, cessation of sweating, lactic acidosis, hypocalcemia, myoglobinuric renal failure.

**HEMODYNAMIC INJURIES:**

• **CARBOXYHEMOGLOBIN**: Carbon monoxide bound to hemoglobin.
  - Results:
    - Cherry red tissues.
    - Hypoxic injury to brain, liver, renal tubules.

• **CYANIDE POISONING**: *In contrast to carboxyhemoglobin*, cyanide will also show cherry red tissues because the blood is fully oxygenated.
  - Cyanide binds to *Cytochrome Oxidase*, thus inhibiting cellular respiratory, such that poisoned cells cannot use O2.

• **ASPHYXIA**: Lack of respired oxygen.
  - Causes:
    - Mechanical (strangulation)
    - Traumatic (Violent thoracic compression)
    - Drowning

• **HIGH ALTITUDE SYNDROME**: Systemic hypoxia, resulting in loss of consciousness, circulatory / respiratory collapse, death, long-term compensatory polycythemia.

• **OXYGEN TOXICITY**:
  - **Respirator Lung**:
    - Intra-alveolar fibrin
    - Hyaline membranes
    - Septal edema and fibrosis
    - Alveolar cell hyperplasia
  - **Retinal Fibroplasia**: Retinopathy that occurs with premature infants given oxygen.

**DRUGS / DRUG-INTERACTIONS:**

• **ADVERSE DRUG REACTION**:
  - **CLINDAMYCIN**: Antibiotic treatment can result in overgrowth of *Clostridium Difficile*, leading to *Pseudomembranous Colitis*.
  - **SALICYLISM**: Salicylate poisoning
    - Respiratory Alkalosis followed by metabolic acidosis.
    - Erosive gastritis
    - Inhibition of platelets
    - Interstitial nephritis, renal-papillary necrosis
    - Reye's Syndrome
  - **SLE-LIKE SYNDROME**: Procainamide, Hydralazine.
    - Clinically looks like SLE, but due to autoimmune reaction to the drug.
    - Goes away after discontinuation of medication.

• **ANTINEOPLASTIC AGENTS**: Alkylating agents, antimetabolites
  - Consequences:
    - Bone marrow suppression
    - Immunosuppression
    - Initiation of cancer

• **IMMUNOSUPPRESSIVE AGENTS**:
  - Examples: Corticosteroids, Cyclosporine, Azathioprine.
• **BIOTRANSFORMATION**: Metabolism of drugs to active (or toxic) form by liver enzymes.
  - Ethylene Glycol is transformed to Oxalic Acid, which is then toxic to:
    - Kidneys
    - CNS
    - Cardiorespiratory
  - Methyl Alcohol $\rightarrow$ Formaldehyde $\rightarrow$ Formic Acid, which may cause
    - Blindness (due to retinal receptor cell degeneration)
    - Brain swelling.

• **ILLICIT DRUGS**:
  - **HEROIN**:
    - Produces true addiction.
    - OVERDOSE: respiratory depression, ARDS, pulmonary edema.
    - Infections occur with prolonged use (needles)
  - **COCAINE**:
    - Produces tolerance and withdrawal
    - OVERDOSE: Cardiac arrhythmia may result in sudden death
  - **AMPHETAMINES**:
    - OVERDOSE: Seizures and cardiac arrhythmias.
  - **PHENCYCLIDINE (PCP)**
    - OVERDOSE: Deep coma or seizures
  - **LYSERGIC ACID (LSD)**
    - OVERDOSE: Large overdose causes coma, convulsions, respiratory arrest.
  - **FINGERNAIL POLISH / GLUES**:
    - Active Ingredients: Benzene, CCl$_4$, Acetone, Toluene

• **FETAL ALCOHOL SYNDROME**:
  - Growth retardation
  - Characteristic facial features (epicanthal folds)
  - CNS dysfunction

• **FETAL TOBACCO SYNDROME**:
  - Low birth weight: 200 grams lighter (light for gestational age)
  - Increased perinatal mortality, due to:
    - Increased risk of *abruptio placentae*
    - placenta previa
    - uterine bleeding
    - **Premature Rupture of Membranes (PROM)**

**INDUSTRIAL POLLUTANTS:**

• **AIR POLLUTION**:
  - **ASBESTOS**: Causes Pneumoconiosis, or Pulmonary Interstitial Fibrosis.
    - Other effects: Pleural fibrous plaques, malignant mesothelioma, lung carcinoma (particularly in smokers).
  - **CAUSTIC AGENT**: Corrosive agent such as concentrated NaOH.
    - Produces gastroesophageal and respiratory necrosis when ingested. Immediately damages the mucosa it contacts.
  - **MERCURIALISM**:
    - **MINAMATA DISEASE**: Organic compounds of Mercury (Hg) can produce CNS damage.
      - Inorganic Mercury causes:
        - Renal tubular necrosis, membranous glomerulonephritis
        - Gingivitis
  - **PLUMBISM**: Lead poisoning
    - Sources: Paint, gasoline combustion
    - Effects:
      - CNS: Peripheral neuropathy, encephalopathy
      - Kidneys: Renal Tubular Acidosis leading to **Fanconi's Syndrome**
      - Hematopoietic:
        - Anemia with decreased erythropoiesis
        - Hemolysis
        - **Basophilic Stippling** of red cells.
  - **RADON**: Indoor gas linked to lung cancer, but it isn't proven.
NATURAL ENVIRONMENTAL POISONS:

- **AMINATA PHALLOIDES**: Toxic mushroom
  - Consequences:
    - Gastroenteritis
    - Hepatic hemorrhagic necrosis
    - Renal tubular necrosis
    - CNS changes
- **ARTHROPOD BITE**
  - Most common insects in US: Brown recluse spiders, black widow spiders, ticks, scorpions.
  - Effects:
    - Direct toxic effects
    - Allergic anaphylaxis (bees)
    - Transmission of infectious disease
- **REPTILE BITE**: Rarely fatal
  - Coral snakes have four venom factors:
    - Neurotoxic
    - Spreading
    - Digestive
    - Hemorrhagic
  - Pit viper snakes: Primarily hemolytic
  - Gila Monster: Local tissue destruction.

GENERAL NUTRITION / NUTRITION DISORDERS:

- **CACHEXIA**: General muscle wasting, as seen in Marasmus.
- **EMACIATION**: Excessive leaness. A wasted condition of the body.
- **DIABETES TYPE II**: Adult onset hyperglycemia, reflects down-regulation of insulin receptors.
  - 80% of patients are obese.
- **ALCOHOLISM**:
  - Selected chronic complications:
    - Mallory-Weiss tear of Esophagus
    - Acute rhabdomyolysis
    - Testicular atrophy
    - GERD
    - PUD
    - Wernicke / Korsakoff
    - Nutritional deficits
- **DIVERTICULOSIS**: Herniation of mucosa and submucosa through muscular layers of the colon. Occurs with chronic low fiber diets.
- **GOITER**: Iodine deficiency leading to hypothyroidism, increased TSH, and hyperplasia of Thyroid gland.
- **KWASHIORKOR**: Protein malnutrition with adequate carbohydrate.
  - Growth failure
  - Skin depigmentation and Hair changes
  - Fatty liver
  - Ascites
- **MARASMUS**: Malnutrition
  - Muscle wasting
- **MEGALOBLASTIC ANEMIA**: Most commonly caused by impaired DNA synthesis, as a result of Vitamin-B12 or Folate deficiency.
  - Large nucleated progenitors of RBC's (immature) stuck in bone marrow. Large oval erythrocytes in the periphery.
- **OBESITY**: 20% or more above mean body fat
  - Diabetes Type II is most important complication
  - Atherosclerosis, MI
  - Gallstones
  - Gout
  - Varicose Veins
  - Oligomenorrhea
WATER-SOLUBLE VITAMINS:

• **VITAMIN B1 -- THIAMINE**:
  o Function: Thiamine Pyrophosphate (TPP) -- it is phosphorylated twice by ATP to get to its active form. Functions in active aldehyde transfers.
  o DEFICIENCY:
    ▪ **WERNICKE'S ENCEPHALOPATHY**
      ▪ Classic Triad of Symptoms:
        ▪ **Ophthalmoplegia** -- paralysis of eye muscles
        ▪ **Ataxia** -- lost muscular coordination
        ▪ **Mental Confusion**
    ▪ **BERIBERI**: Nutritional deficiency of polyneuropathy, edema, and high output cardiac failure.
      ▪ **WET BERIBERI**: Referring to symptoms of edema and high output cardiac failure
      ▪ **DRY BERIBERI**: Referring to polyneuropathy.

• **VITAMIN B2 -- RIBOFLAVIN**:
  o ACTIVE FORMS
    ▪ **FMN**: Add one phosphate to the terminal OH-Group.
    ▪ **FAD**: Add one phosphate to terminal OH-group, plus an AMP
  o DEFICIENCY:
    ▪ Dermatitis, Glossitis
    ▪ Anemia
    ▪ Chaelosis

• **VITAMIN-C: ASCORBIC ACID**
  o SPECIFIC REACTIONS: Covalent Hydroxylation Reactions
    ▪ Formation of hydroxylysine and hydroxyproline in collagens
  o Anti-Oxidant
  o DEFICIENCY: **SCURVY**
    ▪ **ROSARY**: Prominence of costochondral junction in children, seen in scurvy and rickets.
    ▪ **Hemorrhagic Diathesis**: Predisposition to disease in joints, skin, sublingual
    ▪ Tooth loss, gingivitis
    ▪ Inability to limit infections, poor wound healing
    ▪ poor growth

• **VITAMIN B6 -- PYRIDOXINE**:
  o FUNCTION: Forms stable, yet transient Schiff-Base Complexes with amines.
  o Deficiency:
    ▪ CNS disturbance: excitability, convulsions.
    ▪ Hypochromic microcytic anemia.

• **NIACIN**:
  o DEFICIENCY: **PELLAGRA**, characterized by the 3 D's: Dermatitis, Diarrhea, Dementia
    ▪ May also find glossitis
    ▪ Degeneration of the posterior and lateral columns of the spinal cord.

• **VITAMIN B12 -- COBALAMIN**
  o DEFICIENCY:
    ▪ Leads to **PERNICIOUS (MEGALOBLASTIC) ANEMIA**, usually from Type-A Gastritis against Parietal Cells (intrinsic factor) in stomach.
      ▪ Can be caused by lack of **intrinsic factor** in the intestine (that is what absorbs Vitamin B12 in intestine)
    ▪ **Subacute Combined Degeneration**: Demyelination of ascending and descending tracts of the spinal cord.
    ▪ **Glossitis** of tongue.

• **FOLATE**:
  o FUNCTION: **One-Carbon transfers**, in the form of Tetrahydrofolate.
  o DEFICIENCY: **PERNICIOUS (MEGALOBLASTIC) ANEMIA** -- abnormal DNA structure due to insufficient nucleotide synthesis leads to chromosomal abnormalities in the RBC’s.
    ▪ Has been linked to neural tube defects. Adequate amounts must be taken during pregnancy.
    ▪ **Homocystinemia** is elevated homocysteine, which can result from no folate.
FAT-SOLUBLE VITAMINS

• **VITAMIN A: RETINOL**
  - FUNCTIONS:
    - Retinal (aldehyde) -- Visual Cycle.
  - VITAMIN-A TOXICITY: An excess of *all-trans Vitamin-A in the diet* -----> *teratogenic birth defects.*
    - beta-CAROTENE is NOT TOXIC!! -- only Vitamin-A is toxic. beta-Carotene is probably not toxic because the initial Dioxygenase (cutting) step is regulated.
  - DEFICIENCY:
    - **FOLLICULAR HYPERKERATOSIS**: Skin disorder resulting from squamous metaplasia, and occlusion of sebaceous glands.
    - **KERATOMALACIA**: Softening of the cornea, increasing vulnerability to ulcerative and bacterial infections, which may lead to blindness.
    - **XEROPHTHALMIA**: Dry eyes. Squamous metaplasia of conjunctiva and tear ducts, leading to dryness of cornea and conjunctiva.
      - Squamous metaplasia of other locales too.
    - **NIGHT BLINDNESS**

• **VITAMIN E: alpha-TOCOPHEROL**
  - FUNCTION: Only one function -- as an *anti-oxidant.*
    - It will protect poly-unsaturated fats, cholesterol, and rods and cones, from radical oxidation.
    - Importantly, it is a fat-soluble anti-oxidant whereas Ascorbic Acid is water-soluble. So Vit. E gets into membranes.
  - DEFICIENCY: Rare, results:
    - Hemolytic anemia, thrombocytosis
    - Edema in premature infants

• **VITAMIN K: PHYLLLOQUINONE**
  - FUNCTION: The enzymes which use these calcium-chelating residues are CLOTTING FACTORS and enzymes involved in bone-mineralization and demineralization.
  - DEFICIENCY: Diminished clotting factor activity, leading to hemorrhagic diathesis.

• **VITAMIN D: CHOLECALCIFEROL (D3)**
  - SYNTHESIS of 1,25-(OH)2-D3, or 1,25-DIHYDROXYCHOLECALCIFEROL: Vitamin-D is not strictly a vitamin because we can synthesize it ourselves.
    - **SKIN**: Cholesterol -----> Cholecalciferol is a non-enzymatic cleavage catalyzed by UV-LIGHT.
    - **LIVER**: 25-Hydroxylase puts a hydroxyl group on the side chain.
    - **KIDNEY**: 1alpha-Hydroxylase puts a hydroxyl at the 1alpha position.
  - FUNCTION OF VITAMIN-D3: It is stimulated by Parathyroid Hormone, and it promotes the release of Calcium into the blood.
    - *Ialpha-Hydroxylase* in the Kidney is tightly regulated. Parathyroid hormone will allow that reaction to occur, so Vitamin-D gets to its final form.
    - ACTION on INTESTINE: Vitamin-D promotes uptake of more calcium and phosphate in the intestine.
    - ACTION on LONG BONES: Will stimulate osteoclasts to break down hydroxyapatite and release calcium into blood.
  - DEFICIENCY:
    - **OSTEOMALACIA**: In adults, inadequate mineralization of newly formed bone matrix.
    - **RICKETS**: In children, inadequate mineralization of bone and also inadequate cartilaginous mineralization at the growth plate.
      - **ROSARY**: Prominence of the costochondral junction in children, may be seen with Rickets.

MINERALS:

• **FLUORINE**: Deficiency results in dental caries.
  - Tooth enamel contains fluoroapatite

• **IRON**
  - DEFICIENCY: *Microcytic Hypochromic Anemia,* caused by lost blood usually.

KOILONCHIJA: Dystrophy of fingernails, in which they take a spoon shape.
ONCOLOGY

SPECIFIC TUMORS: Only the ones that aren't obvious.

- Striated Muscle Tumors:
  - RHABDOMYOMA: Benign
  - RHABDOMYOSARCOMA: Malignant (more common)

- Smooth Muscle Tumors:
  - LEIOMYOMA: Benign
    - Leiomyoma of Uterus: Benign tumor of uterus presents with abdominal pain and dysmenorrhea.
  - LEIOMYOSARCOMA: Malignant

- Melanocytes:
  - A NEVUS is a benign tumor
  - MELANOMA is malignant.

- MIXED TUMORS: Derive from a cell that is multipotent.
  - PLEOMORPHIC ADENOMA: BENIGN tumor of the salivary gland. It has epithelial, bone, and cartilage components.
    - Malignant Mixed Tumor of Salivary Gland is the name for the malignant tumor.
  - WILMS'S TUMOR: NEPHROBLASTOMA. Mixed tumor of renal tissue.

- Germ-Cell Tumors:
  - TERATOMA: Tumor composed of tissues derived from all three germ layers. It usually occurs in gonads.
    - DERMOID: Benign teratoma of the ovary, having all sorts of strange tissue in it.
  - TERATOCARCINOMA: Malignant tumor. Also Seminoma.
  - SEMINOMA: A malignant tumor of germ cells.
  - DIAGNOSIS: High levels of hCG and AFP are diagnostic of teratoma.
    - Neoplastic germ cells secrete hCG
    - Neoplastic yolks cells (found in Teratoma) secrete AFP.

- MENINGIOMA: A BENIGN meninges tumor. It can be deadly because it can compress on the brain.

Random Tumor Vocabulary (RTV):

- SARCOMA: A tumor that has arisen from connective tissue or mesothelium.
- CARCINOMA: A tumor that has arisen from epithelial tissue.
  - CARCINOMA IN SITU: An epithelial tumor that has not yet penetrated the basement membrane and thus has no current chance of metastasis.
- ADENOMA: Benign tumor of glandular epithelial tissue, such as a tubular adenoma of the colon.
  - PEDUNCULATED ADENOMA: An adenoma with a stalk, or peduncle, protruding from the mucosal surface.
  - SESSILE ADENOMA: An adenoma without a stalk.
  - POLYP: Any growth or mass protruding from a mucous membrane.
  - Abnormal cells are elongated and cannot produce mucin anymore.
- PAPILLOMA: Benign tumor of non-glandular epithelial tissue.
- HAMARTOMA: Disorganized, benign tumor-like nodule.
  - It contains differentiated cells, but it is disorganized, and one cell type often predominates (although not exclusively).
- CELLULAR MORPHOLOGY / HISTOLOGY:
  - METAPLASIA: The replacement of one adult cell by another adult cell. Change of cell-type.
    - Squamous Metaplasia: Glandular epithelium ------> squamous epithelium.
    - Barrett Esophagus:
      - DYSPLASIA: An Altered growth, altered development.
      - ANAPLASIA: Lack of differentiated features in a cancer cell, indicative of malignancy.
      - DESMOPLASIA: Connective tissue proliferation in response to cancer.
- CHORISTOMA: The presence of normal tissue in an abnormal location.
DIAGNOSIS of MALIGNANCY:

- HISTOLOGICAL DIAGNOSIS:
  - ANAPLASIA
    - Pleomorphism: Variation in the size and shape of cell nuclei.
    - Enlarged and hyperchromatic nuclei
    - Prominent nucleoli
  - Increased Nuclear to Cytoplasmic Ratio.
  - Bizarre Cells and Giant Cells.
  - MITOTIC ACTIVITY: Mitotic figures and atypical mitoses.
- GROSS-APPEARANCE: Malignant tumors have irregular edges, or star-shaped jutting borders.
- INVASION: Demonstration of the tumor invading basement membrane, blood vessels, or lymphatics, is diagnostic of malignancy.

GRADING AND STAGING OF TUMORS:

- CANCER GRADING: Histological assessment of malignancy.
  - GRADE 1: Well differentiated
  - GRADE 2: Medium differentiation.
  - GRADE 3: Poorly differentiated.
- CANCER STAGING: Clinical assessment of the spread of the tumor, based on TNM system.
  - (T) TUMOR SIZE
    - Graded 1-4. 1 is the mildest.
  - (N) NODAL: Has it spread to any lymph nodes? Graded 0-3
    - N0: It has no spread to lymph nodes.
    - N3: Most severe spread to lymph nodes.
  - (M) METASTASIS
    - M0: No metastases are present.
    - M1: Metastases are present.
- DUKE'S CLASSIFICATION: Method of staging colon cancer.

CARCINOGENESIS:

- INITIATION: Irreversible damage to DNA in a critical target gene.
  - Initiation is a permanent genetic alteration (mutation) of the cell and is thus irreversible.
- PROMOTION: Single initiated cell is selected for and promoted into a benign tumor.
  - Promotion is reversible. It requires continual (or repeated) stimulation, irritation, or treatment, in order to maintain the promoted state.
- PROGRESSION: The process by which a benign neoplasm is transformed into malignant cells.
  - INVASION (STAGE I): Contiguous growth of the tumor.
    - Carcinoma In Situ: A malignant epithelial tumor that has not yet penetrated the basement membrane.
    - PROCESS: Step by step invasion.
      - Penetrate Basement Membrane: Collagenases and proteases.
      - Binding to the extracellular matrix: integrins, fibronectin.
      - Degradation of extracellular matrix.
      - Secrete extracellular proteases that break down Collagen IV, Proteoglycans.
      - Movement through interstitial tissues: Autocrine motility factor induces movement by pseudopodia.
  - METASTASIS (STAGE II): Spread of the tumor to a non-contiguous site, through blood or lymph.
    - HEMATOGENOUS METASTASES: Metastasis through blood. Most frequent target sites are liver and lung.
    - LYMPHATIC METASTASES: Regional enlargement of lymph nodes can be signs of lymphatic metastasis.
    - PROCESS:
      - Invasion of Circulation:
      - Escape from Circulation: Adherence to endothelia, bind to basement membrane, extravasation.
      - Angiogenesis and local growth: Growth of metastatic tumor and its blood supply.
IMMUNODIAGNOSIS of CANCERS: The origin of cancers that are histologically unidentifiable can be diagnosed by immunohistology.

- **Keratins:** Indicates the presence of epithelial cells: carcinoma or mesothelioma.
- **Desmin:** Indicates a tumor of muscle origin: myoma.
- **Vimentin:** Indicates tumors of mesenchymal origin: sarcomas.

AMES TEST: Test for mutagenesis, by measuring the number of backward (reversion) mutations in His' *Salmonella* cells grown without Histidine.

- All carcinogens are also mutagens. Most mutagens are also carcinogens.
- Introduce Rat-Liver **Microsomal Oxidases** into the bacterial culture. These enzymes are added in order to metabolize the potential carcinogens (mutagens), as most require metabolic activation before becoming mutagenic.
- **RESULTS:** The more bacterial colonies you get, (bacteria living on the His` bare medium), the greater the mutagenicity of the compound being tested.

ENVIRONMENTAL CAUSES OF CANCER:

- **CHEMICAL CARCINOGENS**
  - **DIRECT-ACTING CARCINOGENS:** Do not need to be metabolized in liver. They are generally **Electrophilic** and thus attracted to the negatively charged substituents in the nucleus.
    - **NITROGEN MUSTARD:** A cancer (chemotherapy) drug, that is ironically also carcinogenic itself.
    - **Benzyl Chloride**
    - **Nitrosylmethylurea**
  - **INDIRECT-ACTING CARCINOGENS:**
    - **CISPLATIN:** Chemotherapy drug that is ironically carcinogenic itself.
    - **Anabolic Steroids** can cause brain and liver cancer
    - **POLYCYCLIC AROMATIC HYDROCARBONS (PAH):** Produced by incomplete combustion of organic material. Charred meat, for example.
      - **METABOLISM:** **Cytochrome-P450 Mixed Oxidase** in liver microsomes.
      - **Aryl Hydrocarbon Hydroxylase:** PAH -----> 7,8-Epoxide
      - **Epoxide Hydrase:** 7,8-Epoxide -----> 7,8-Diol
      - **Aryl Hydrocarbon Hydroxylase:** 7,8-Diol -----> 7,8-Diol-9,10-Epoxide, the reactive carcinogenic product.
    - **Epoxide:** The final reactive carcinogenic product is an epoxide.
    - **AFLATOXIN-B1:** Product of *Aspergillus* mold, found in moldy grains in other countries.
      - **RISK:** Far increased risk for Hepatocellular Carcinoma.
      - **METABOLISM:** **Mixed-Function Oxidase** with an **Epoxide Intermediate**, very much like PAH.
    - **AROMATIC AMINES, AZO DYES:** Their metabolites are excreted in the urine, where they can cause **bladder cancer**.
    - **NITROSAMINES:**
      - **METABOLISM:** They originate as Nitrites found in food-preservatives. They form nitrosamines by reacting with acids in stomach.
  - **METALS:** Occupational hazards, leading to lung cancer.

- **PHYSICAL CARCINOGENS:**
  - **UV-RADIATION**
    - **UV-A:** Lower energy UV-light, comprising 97% of UV radiation.
      - It is longer wavelength and penetrates the skin to a greater depth than UV-B. It is not innocuous.
    - **UV-B:** Implicated in skin cancer. Wavelength below 400nm.
      - This is only about 3% of UV light.
      - **MECH:** Formation of **Thymine-Thymine Dimers** in DNA → resulting in a deletion.
    - **UV-C:** Absorbed by the ozone layer, so we don't come into contact with it.
  - **IONIZING RADIATION**
  - **ASBESTOS:** Made of silicates and rigid fibers.
    - **RISK:** Linked to **Mesothelioma** of the pleural and peritoneal cavities.
  - **FOREIGN BODIES**
• **VIRAL CARCINOGENS:**
  - Animal Viruses: Experimental animals
    - **Rous Sarcoma Virus:** Virus contains an oncogene, induced cancer in chickens.
    - **Shope Papilloma Virus** caused papillomas in rabbits.
    - **SV40 Virus:** Member of the polyoma virus family, which originates from African monkeys. Induces cancer in mice and rats, but not known to in humans.
  - **HUMAN PAPILLOMA VIRUS (HPV):**
    - **STRUCTURE:** Circular double-stranded DNA Virus
    - **SUBTYPES:**
      - **HPV-1, HPV-2:** Lead to epithelial warts.
      - **HPV 6, 11, 16, 18:** All lead to Genital Warts
      - **HPV 16, HPV 18:** Associated with increased risk for **Cervical Cancer**, and cancer of Penis, Vulva.
        - Also, **Perianal condylomata** are found with HPV.
      - **MECH:** HPV is known to cause cancer by blocking tumor-suppressor genes.
        - **E6** is an HPV protein that can bind the retinoblastoma gene to inactivate it.
        - **E7** is an HPV protein that can bind p53 to inactive it.
  - **EPSTEIN-BARR VIRUS (EBV):**
    - **RISKS:**
      - **NASOPHARYNGEAL CARCINOMA**
      - **BURKITT'S LYMPHOMA:** EBV infects B-Lymphocytes.
        - Disease is common in childhood.
        - It occurs in regions where Malaria is endemic.
        - EBV is found in all Burkitt's Lymphoma's in Africa, and about 20% of them in USA.
        - Also can be caused by a translocation (see below).
      - **HODGKIN'S DISEASE:** EBV is found in about 50% of these cases.
      - **INFECTIOUS MONONUCLEOSIS** is caused by an acute EBV infection.
  - **HEPATITIS-B VIRUS (HBV)**
    - **STRUCTURE:** Partial double-stranded, partial single-stranded DNA virus.
    - **RISK:** Hepatocellular Carcinoma. Especially in Asia and Africa.
      - *The level of risk is synergistic with the carcinogenic effects of Aflatoxin-B1.*
    - **MECH:** Hepatitis Virus codes for proteins that block Tumor Suppressor proteins.
      - **HBX** is a protein encoded by HBV. It blocks activation of **P53**.
    - **Hepatitis-C Virus** is also associated with increased hepatoma risk.
  - **POLYOMA VIRUSES:**
    - **STRUCTURE:** Small circular double-stranded DNA virus.
    - **BK Virus** is being studied for oncogenicity, due to its known relatedness to the SV40 virus.
    - **JC Virus** is also being studied.
  - **HUMAN T-CELL LEUKEMIA VIRUS I and II (HTLV-I and II):** The only known oncogenic Retrovirus. Associated with rare T-Cell Leukemias in Japan and Carribean.

**ONCOGENES:** These genes show _dominant_ transmission. The presence of only one aberrant copy is sufficient to produce cancer.

• **PROTO ONCOGENES:**
  - **c-onc:** A human (cellular) proto-oncogene, that codes for proteins that regulate cell division and growth. If these protein lose their regulation or are overexpressed, they become oncogenic.
  - **v-onc:** A proto-oncogene that has been incorporated (via transduction) into a virus, thus making it lose its regulation and become oncogenic.

• **TRANSFORMING VIRUSES:** Two basic mechanisms of viral onogenesis.
  - **ACUTE TRANSFORMING VIRUSES:** The virus has transformed a copy of the oncogene (now called v-onc) into its own genome. When the virus spreads, it takes the oncogene with it and can cause aberrant expression of the gene in infected cells.
  - **SLOW TRANSFORMING VIRUSES:** Insertional Mutagenesis of a proto-oncogene. The virus does not have a v-onc, but rather mutates a c-onc by virtue of its insertion into genome.

• Activation of Proto-oncogenes
  - **ACTIVATION BY MUTATION**
    - **Ras GENES:** They code for GTP-binding proteins, **G-Proteins**
• Ras SUBTYPES:
  ▪ Harvey-Ras: Initial discovered Ras, discovered to be mutated in bladder-cancer patient.
  ▪ Kirsten-Ras
  ▪ N-Ras
• RISK: Colorectal Cancer, Pancreatic Cancer
• p21 PROTEIN is the name of the G-Protein encoded by Ras. It is mutated (point mutation) in 30% of all human cancers.
  
  o ACTIVATION BY TRANSLOCATION
    ▪ c-myc: This oncogene (Chrom 8) translocates to Chromosome 14, which codes for an Ig Heavy Chain (C\textsubscript{H}) region. This translocation results in over expression of the oncogene.
    ▪ MECH: c-myc is activated by its proximity to the heavy-chain gene. This results in a dominant monoclonal colony of B-Cells, which are selected for based on the mutation.
    ▪ RISK: BURKITT'S LYMPHOMA is found to have the translocated c-myc gene in ABOUT 75% of cases.
      ▪ In the other 25% of cases, an Immunoglobulin light chain is translocated to Chromosome 8, from Chrom 2 or 22, and causes a similar effect.

  ▪ PHILADELPHIA CHROMOSOME: abl (Chrom 9) and bcr (Chrom 22) translocation.
    ▪ MECH: abl is fused to bcr on Chromosome 22, such that bcr drives the over expression of the abl gene.
    ▪ bcr codes for Tyrosine Kinase Activity. Hyper activation leads to cancer.
    ▪ RISK: CHRONIC MYELOGENOUS LEUKEMIA (CML)

  o ACTIVATION BY GENE AMPLIFICATION: Increase in the number of copies of a gene.
    ▪ Cytologic Findings: These two chromosomal conditions are interchangeable.
    ▪ HOMOGENOUS STAINING REGIONS (HSR's) are visible in double-minute chromosomes.
    ▪ DOUBLE-MINUTE CHROMOSOMES are the converse cytological finding, also found.
    ▪ RISK:
      ▪ N-myc HSR's are seen in Neuroblastoma
      ▪ HER-2/neu is a growth-factor receptor. When it is amplified, it is associated with poor prognosis.

  ▪ NEUROBLASTOMA:
    ▪ Most common tumor in early childhood.
    ▪ Tumor arises from sympathetic neural tissue.
    ▪ The degree of N-myc

• Different roles of Oncogenes:
  
  o ONCOGENES AND GROWTH FACTORS
    ▪ MECH: Genes that code for things like PDGF, which is believed to cause autocrine growth stimulation in neoplastic cells.
    ▪ v-sis: Retroviral oncogene that codes for a protein very similar to PDGF beta-chain.
    ▪ c-sis: Proto-oncogene that produces the actual PDGF beta-chain.
    ▪ RISK: Sarcomas and Glioblastomas produce PDGF, whereas normal cells do not.
    ▪ STOMACH CANCER: Fibroblast Growth Factor (FGF) is overexpressed in stomach cancer.

  o ONCOGENES AND GROWTH-FACTOR RECEPTORS: Implicated in cancer due to their strong signal-transduction role in promoting cell-growth.
    ▪ MECH: Lots of oncogenic receptors are TYROSINE-KINASE RECEPTORS
    ▪ EXAMPLES:
      ▪ v-erb B: Oncogene that codes for a variant of the EGF-Receptor
      ▪ HER2/neu: Codes for NGF-Receptor. It also has Tyrosine Kinase activity.
        ▪ RISK: This is overexpressed in BREAST, OVARIAN, ENDOMETRIAL CANCER.
        ▪ The protein level in these cancers correlates with prognosis.

  o ONCOGENES AND MEMBRANE PROTEIN-KINASES
    ▪ TYROSINE KINASE activity is implicated in lots of proto-oncogenes.
      ▪ c-abl: Gene codes for a tyrosine kinase.
        ▪ It is overexpressed by its translocation next to the bcr gene.
      ▪ c-src: Gene codes for a tyrosine kinase.

  o ONCOGENES AND G-PROTEINS
- **Ras** codes for P21 G-Protein.
  - MECH: Ras usually undergoes point mutation at codon 12 or 61.
    - Ways in which Ras mutation leads to cancer: anything that makes the GTP-bound state more persistent.
      - Loss of intrinsic GTPase activity \(\rightarrow\) G-Protein is constitutively turned on.
      - Loss of sensitivity to GTPase Activating Protein (GAP) \(\rightarrow\) G-Protein is constitutively turned on.
      - Increased exchange of GDP for GTP.
  - RISK: Again, Colorectal and Uterine cancers.
  - SIGNAL TRANSDUCTION: Ras \(\rightarrow\) Raf \(\rightarrow\) Mapk (Mitogen-Activated Protein Kinases)

**ONCOGENES AND NUCLEAR REGULATORY PROTEINS**

- **c-myc** and **c-fos**: Competence Proteins. Nuclear regulatory proteins involved in taking the cell out of G0, thereby enabling it to resume the cell cycle when properly stimulated.
  - PDGF stimulation causes these proteins to be expressed \(\rightarrow\) making them competent to receive further signals which allow them to undergo mitosis.
  - EGF or IGF is then needed to take the cell through S-Phase and mitosis.

**TUMOR-SUPPRESSOR GENES**: These are recessive cancer genes. Both copies must be defective before cancer results.

- **RETINOBLASTOMA GENE**
  - TWO-HIT HYPOTHESIS: If you inherit one bad copy of the gene, then you will almost inevitably get retinoblastoma in both eyes, by effecting a random mutation of the other copy of the gene.
    - A random somatic mutation of one copy is highly likely at some point in life, while a mutation of both copies is unlikely.
  - INHERITED RETINOBLASTOMA is thus is both eyes.
  - SPORADIC RETINOBLASTOMA is thus in one eye -- sporadic mutation (double-whammy) of both copies of the Rb gene.
  - **Rb-GENE**:
    - MECH: Rb-gene codes for a factor that blocks entry of the cell into S-Phase. The Rb-Protein \(pRb\) blocks the E2F growth factor.
      - Normally, pRb gets phosphorylated by cyclins \(\rightarrow\) this makes it let go of E2F \(\rightarrow\) E2F pushes cell into S-Phase.
    - LOCATION: Rb-Gene is located on **Chrom 13**, band q14.

- **P53 GENE**: The guardian of the genome, dammit.
  - LOCATION: **Chrom 17**
  - MECH: The **P53 gene prevents a mutated cell from proliferating**. It is induced in response to DNA damage, and it inhibits the cell from entering S-Phase, and ultimately making it undergo apoptosis.
    - p53 bind cyclin-dependent kinases \(\rightarrow\) induce cyclin-inhibitor WAF \(\rightarrow\) inhibit cyclin \(\rightarrow\) prevent cell division.
  - RISK: P53 mutations are the most common genetic defect found in cancers.

- **WILMS'S TUMOR GENE**: Childhood form of renal cancer.
  - It is known to be a tumor-suppressor gene, because loss of heterozygosity leads to cancer. Function of the gene-product is unknown.

- **DCC SUPPRESSOR GENE**: Detected in Colon Carcinoma
  - MULTIPLE genetic steps in sequence are involved in Colon Carcinoma:
    - Adenomatous Polyposis Coli gene is mutated.
    - k-Ras gene is mutated.
    - DCC suppressor gene then is mutated.
    - p53 gene may become mutated.

- **BRCA1**: Recently identified BREAST-CANCER Tumor-Suppressor gene.
  - 85% of breast cancers are sporadic.
  - The other 10-15% of familial breast cancers (predisposition) may be due to heterozygosity in this gene.

**XERODERMA PIGMENTOSUM**: Autosomal-Recessive Disorder, in which people have defective DNA-Repair mechanisms. This leads to a very high incidence of cancer.

**CLINICAL LECTURE**:

- **CLARK'S LEVELS**: Five levels for staging Melanomas, according to how deep it goes down.
LEVEL I: In-Situ Carcinoma. The disease is still confined to the epidermis.
- Measured depth is far less than 0.75mm
LEVEL II: Early penetration into the Papillary Dermis.
LEVEL III: Deeper penetration into Papillary Dermis.
LEVEL IV: Well into the Reticular Dermis.
LEVEL V: Into subcutaneous tissues.
- Measured depth will be greater than 4mm

BREAST CANCER:
- Diagnosing Malignancy
  - X-RAY: Malignant biopsy shows clustering with linear pattern to branches.
  - Stellate shaped calcifications.
  - HISTO: Different cell-types on the slide would favor a benign tumor. Singular cell-types would be malignant.
- Ductal Carcinoma In Situ (DCIS): Early Stage I lesion, with no (current) chance of metastasis.
  - Cribriform Carcinoma: Low-grade DCIS. Well-differentiated.
  - Comedo form Carcinoma: Tremendously enlarged, solid mass with impending necrosis in the middle. High-grade DCIS, but it is still In Situ, so it is still Stage I

CLONAL ORIGIN OF CANCER: Most cancers arise from a single transformed cell.

- Multiple Myelomas arise as a single lineage of B-Cells, with monoclonal antibodies.
- Experimental Evidence: Uterine Tumors in women express only one allele of Glucose-6-Phosphate Dehydrogenase, even though these women normally have two alleles of it.
  - G6PD is an X-chromosome gene. Normally in heterozygotes, half of cells will express one isozyme and the other half express the other isozyme.
  - In Uterine tumors, all cells express the same isozyme, indicating that they all derived from a single cell.

Cancer as Altered Differentiation:
- Squamous Cell Carcinoma
- Teratocarcinoma
- Leukemias and Lymphomas

TUMOR IMMUNOLOGY: There is little evidence that immunological defenses play a significant role in fighting cancer in humans. Experimental evidence comes mostly from animals.

- TUMOR-SPECIFIC ANTIGENS (TSA): Novel antigens produced only by cancer cells. They differs according to cause of the cancer.
  - CHEMICALLY-INDUCED TUMORS: They make a UNIQUE tumor-specific antigen, unique to each tumor.
  - VIRALLY INDUCED TUMORS make a COMMON tumor-specific antigen. Each tumor created by the same virus will yield the same antigen.
- TUMOR-ASSOCIATED ANTIGENS: Those expressed initially in the embryo but then arrested in the adult.
  - They can then show up again in a tumor, thus they are called Oncodevelopmental Antigens.
  - These antigens are measured clinically to test for tumor re-emergence:
    - Carcinoembryonic Antigen EA (CEA): Can be measured to follow the re-emergence of a tumor.
    - alpha-Fetoprotein is measured in testicular cancers.
    - CA125 is measured in ovarian cancers.

Mechanisms of Cytotoxicity:
- T-Cell mediated Cytotoxicity
- NK-Cell Cytotoxicity: Mediated by lymphokines and lymphokine-activated killer cells.
- Macrophages
- Antibody-dependent Cytotoxicity (ADCC)
- Complement-mediated Cytotoxicity

IMMUNODEFICIENCY: It increases your risk for B-Cell Lymphomas

PARANEOPLASTIC SYNDROMES: The systemic effects of cancers in the host that are not due primarily to tumor or its metastases.
• **FEVER**: Especially with Hodgkin's, Renal cell carcinomas, osteogenic sarcomas.
• **ANOREXIA AND WEIGHT LOSS**
• **ENDOCRINE SYNDROMES**
  o **INAPPROPRIATE ANTIDIURESIS**
  o **HYPERCALCEMIA**: About ten percent of all patients. Usually attributed to secreted of a PTH-like peptide by an epithelial tumor.
    ▪ **ECTOPIC HORMONE PRODUCTION** is the inappropriate secretion of hormones from a tumor, which can occur in any tumor regardless of its origin.
    ▪ **CUSHING'S SYNDROME** can result from ectopic production of cortisol.
  o **GONADOTROPIC SYNDROME**
  o **HYPOGLYCEMIA**
• **NEUROLOGIC SYNDROMES**
  o **SPINAL CORD**:
  o **PERIPHERAL**:
• **SKELETAL MUSCLE**
• **HEMATOLOGIC SYNDROMES**:
  o **ERYTHROCYTOSIS**
  o **ANEMIA**: Frequently cause is not understood. Sometimes from tumor bleeding.
  o **THROMBOCYTOSIS** occurs in about one third of patients. Cause unknown.
  o **THE HYPERCOAGULABLE STATE**
    ▪ **VENOUS THROMBOSIS**: Often found in mucin-secreting cancers, such as pancreatic cancers.
    ▪ **DISSEMINATED INTRAVASCULAR COAGULATION (DIC)**
    ▪ **NONBACTERIAL THROMBOTIC ENDOCARDITIS**
• **MALABSORPTION**
• **RENAL SYNDROMES**
• **CUTANEOUS SYNDROMES**

**EPIDEMIOLOGY OF CANCER**

• **CAUSE of DEATH**:
  o Cancer is #2 next to CV disease.
  o Lung cancer is biggest killer in both males and now females in USA.
• **CANCER PREVALENCE**
  o Stomach cancer has gone down. Lung cancer has gone up.
  o Hepatoma and Esophageal cancer are far more common far east.
  o Colorectal and Breast cancer are more common in USA.

**DEVELOPMENTAL AND GENETIC DISORDERS**

**TERATOGEN**: Chemical, physical, or biologic agent that causes developmental anomalies.

• **FIRST TRIMESTER**: Greatest risk. The formation of primordial organ systems is the stage of development most susceptible to teratogenesis.

**ERROR of MORPHOGENESIS**:

• **AGENESIS**: The complete absence of an all or part of an organ primordium.
  o Examples: Agenesis of Corpus Callosum, Agenesis of Kidneys
  o **Sertoli Cell Only Syndrome**: Absence of germ-cells.
• **APLASIA**: Absence of an organ, coupled with the persistence of an organ rudiment that never developed completely.
  o Example: In aplasia of lung, the bronchi end in a blind pouch of nondescript tissue.
• **HYPOPLASIA**: Reduced size owing to incomplete development of all or part of an organ.
  o Examples:
    ▪ **Microphthalmia**: Small eyes
    ▪ **Micrognathia**: Small chin.
    ▪ **Microcephaly**: Small brain and cranium.
• **DYSRAPHIC ANOMALIES**: Defects caused by the failure of apposed structures to fuse.
  o Two examples = **SPINA BIFIDA**, **CLEFT PALATE**
• **INVOLUTION FAILURES**: Persistence of embryonic or fetal structures that should involute at some stage in development.
  o Example = **Persistent Thyroglossal Duct**. Incomplete involution of thyroglossal duct, which connects base of tongue with thyroid.
• **DIVISION FAILURES**: Caused by the incomplete cleavage of embryonic tissues, when that process depends on the programmed death of cells.
  o Example = **Syndactyly**
• **ATRESIA**: Defects caused by the incomplete formation of a lumen.
  o Example = **Esophageal Atresia** = failure to form esophageal lumen.
• **DYSPLASIA**: Abnormal organization of cells into tissues, resulting in abnormal histogenesis.
  o Example = **Tuberous Sclerosis**, in which brain tissue forms abnormally into visible "tubers"
• **ECTOPIA**: Anomaly in which an organ is outside its normal anatomic site.
• **DYSTROPIA**: Retention of an organ at a site where it is located during development.
  o Example = **Pelvic Kidneys, Abdominal Gonads**

**CLINICALLY IMPORTANT MALFORMATIONS:**

• **POTTER COMPLEX**: All of the developmental consequences originating from **OLIGOHYDRAMNIOS** -- a reduced amount of amniotic fluid.
  o **ETIOLOGY**: Potter Complex usually results from failure of development of the fetal mesonephric duct -- **renal agenesis**.
  o **CLINICAL**: The fetus is usually born with a breeched presentation.
  o **ANOMALIES**:
    ▪ Pulmonary Hypoplasia
    ▪ External signs of intrauterine fetal compression.
    ▪ Morphologic changes of the amnion.
    ▪ These morphological features will be found regardless of the cause of the Oligohydramnios.
• **ANENCEPHALY**: Congenital absence of the cranial vault.
  o **CAUSE**: Dysraphic defect of Neural Tube closure.
  o **PATHOGENESIS**: Genetic factors play a role. Risk of a second one goes up after having one anencephalic fetus.
• **NEURAL TUBE DEFECTS**: Failure of neural tube to close.
  o **CRANIORACHISCHISIS**: Neural tube open from cranium into the spinal cord and vertebral column.
  o **SPINA BIFIDA**: Incomplete closure of the spinal cord and vertebral column.
    ▪ **PATHOGENESIS**:
      ▪ Usually localized to lumbar region.
      ▪ It is the mildest of the dysraphic anomalies.
    ▪ **alpha-FETAL PROTEIN (AFP)**: It is often HIGH in Spina Bifida, although this is not a sensitive test. It is a good initial screening test, to test for possibilities of Spina Bifida. AFP can be high for other reasons, too.
  o **MENINGOCELE**: Hernial protrusion of meninges through the vertebral column.
  o **MYELOMENINGOCELE**: Hernial protrusion of meninges and neural tissue through the vertebral column.
• **FETAL ALCOHOL SYNDROME**: Anomalies resulting from consumption of alcohol during pregnancy.
  o **SYMPTOMS**:
    ▪ Characteristic Facial Dysmorphologies
      ▪ Microcephaly, Micrognathia
      ▪ Thin upper lip
      ▪ No Philtrum
      ▪ Epicantal folds
    ▪ Mental Retardation.
    ▪ Growth retardation.
    ▪ Septal heart defects
• **TORCH COMPLEX**: Cluster of similar symptoms occurring from infectious diseases.
  o **TORCH**:
    ▪ **TOXOPLASMOSIS**: Cat shit. Not too common intrauterine, although mothers commonly have **Toxoplasma** antibodies.
- Others
- **Rubella**: Very rare due to vaccine.
- **Cytomegalovirus**: Fairly common. Up to 2% of newborns infected.
- **Herpes Virus**: HSV-II is most often contracted by exposure to open infection passed through birth canal, which can be prevented by C-Section. Infection in-utero is more rare.
  - **Symptoms**: Common TORCH Symptoms
    - Inflammatory lesions of Brain: Most serious problems.
      - Histo: Early necrotic lesions later become calcified and visible on CT, esp. in Toxoplasmosis.
      - **Symptoms**: Psychomotor retardation, neurological defects, seizures.
    - **Ocular Defects**: Particularly in Rubella. Cataracts and microphthalmus.
    - **Cardiac Defects**: Septal defects, patent ductus arteriosus.

**Chromosomal Abnormalities**:

- **Reciprocal Translocations**: Recombination between non-homologous chromosomes, in which whole parts of a chromosome are moved to a different location.
  - Balanced Translocations occur when there is no less of genetic material. These translocations may be silent, although the mother has the risk of passing visible chromosomal abnormalities to offspring.
- **Robertsonian Translocations**: Translocation in which division occur near centromere.
  - **Products**: One very long metacentric chromosome and a small chromosome fragment.
- **Chromosomal Deletions**: Related to several cancers in humans.
- **Chromosomal Inversions**: DNA is flipped around and inserted backwards.
  - **Pericentric inversions** are breaks on opposite sides of the centromere (around the centromere).
  - **Paracentric inversions** are breaks on the same side of the centromere.
- **Ring Chromosomes**: One very long metacentric chromosome and a small chromosome fragment.
- **Isochromosomes**: Faulty division of the chromosome in which it divides in a plana transverse to the mitotic spindle, rather than parallel to it, during Anaphase.
  - Results are chromosomes consisting of two identical arms.
- **Numerical Abnormalities**:
  - Haploid
  - Diploid
  - Euploid
  - Polyploid
  - Aneuploid
  - Monosomy
  - Trisomy
  - **Mosaicism**: Condition caused by Non-disjunction in which the body contains two or more karyotypically different cell lines.
  - **Non-disjunction**: Failure for homologous chromosomes to divide in Anaphase I of Meiosis, resulting in one Monosomic and one Trisomic daughter cell.
    - The monosomic daughter cell is inviable, except for Monosomy X.
    - The trisomic daughter cell may be silent or may result in a variety of abnormalities, depending on which chromosome it is.
- **p**: The short arm of a chromosome
- **q**: The long arm of a chromosome

**Chromosomal Disorders**:

- **Down's Syndrome**:
  - **Cause**: Trisomy 21 is most common cause, although other chromosomes can cause it too.
    - Trisomy 21 usually occurs from non-disjunction, but it can also occur as a result of a Robertsonian Translocation involving chromosome 21.
  - **Risk**: Risk for Down's Syndrome increases sharply with increased age at parturition.
    - Risk goes form 1:1000 at normal, to 1 in 30 by age 45.
  - **Symptoms**:
    - Mental Retardation, worsening with age (from 70 in childhood to 30 in adulthood).
    - Craniofacial Features: Characteristic
      - **Brushfield Spots** are characteristic speckles in eyes.
- **Simian Crease**: Horizontal crease on hands
- **Epicanthal folds**
  - **CONGENITAL HEART DISEASE**: 30% of patients.
  - **GI TRACT**: Duodenal stenosis, atresia
  - **IMMUNE SYSTEM**: Unusually susceptible to disease
  - **HEMATOLOGIC**:
    - Higher risk for Leukemia.
  - **NEUROLOGICAL**: They show strong histological likeness to Alzheimer's Disease by age 35. Similar brain atrophy pattern. Interesting finding.

- **KLINEFELTER'S SYNDROME**: XXY. Tall, sterile, hypogonadic male.
  - **SIGNS**: Low testosterone, High FSH and LH
    - Extra X chromosome will generate the female-typical **Barr Body** (silent X chromosome), visible in most nuclei.
  - **SYMPTOMS**: Gynecomastia, infertility, female pattern pubic hair, testicular atrophy.

- **TURNER SYNDROME**: XO (Monosomy X). Masculine Woman.
  - **PATHOGENESIS**: Many woman are only missing part of the other X chromosome -- not the whole thing.
  - **SYMPTOMS**:
    - No menarche, sterility
    - **STREAK GONAD**: Abnormal development of ovary, resulting in a fibrous streak.
    - Webbed neck
    - They are short.
    - Horseshoe kidney is often seen
    - Coarctation of Aorta seen in 15% of cases.

- **TRISOMY 18 (Edward's Syndrome)**: Increased maternal age is a risk for this.
  - **SYMPTOMS**: Sever congenital abnormalities
    - Prominent occiput, small jaw, clenched hands, rocker bottom feet
    - Profound CNS and heart abnormalities
    - Prognosis only to 1 year of life.
  - **CLINICAL**: If you have a baby with congenital heart problems and you can diagnose this abnormality, then that is good cause not to treat the heart problems too aggressively.

- **TRISOMY 13 (Patau Syndrome)**: Increased maternal age is a risk for this.
  - **SYMPTOMS**: Similar to trisomy 18, but rarer and more severe.
    - Polydactyly and bilateral cleft lip.

- **PRADER-WILLI SYNDROME**: Deletion of part of short arm of the **Paternal copy** of Chromosome 15.
  - An example **Genomic Imprinting**, where the maternal or paternal copy of a chromosome directs different genetic expression, as shown by the different symptoms in their deletion.
  - **SYMPTOMS**:
    - Mental retardation
    - Short stature
    - Hypotonia
    - Obesity and huge appetite after infancy.
    - Small hands and feet
    - Hypogonadism

- **ANGELMAN (Happy Puppet) SYNDROME**: Deletion of part of short arm of the **Maternal copy** of Chromosome 15.
  - An example **Genomic Imprinting**, where the maternal or paternal copy of a chromosome directs different genetic expression, as shown by the different symptoms in their deletion.
  - **SYMPTOMS**:
    - Mental retardation
    - Ataxic gait
    - Seizures
    - Inappropriate laughter

- **CRI DU CHAT SYNDROME**: Classical deletion syndrome. Deletion in the short art of Chromosome 5.
  - **SYMPTOMS**:
    - Infants have a "Cry of the Cat."
    - Mental retardation.
AUTOSOMAL DOMINANT DISORDERS:

- **Heritability:**
  - If one parent has it, the child has a 50% chance of getting it.
  - Gene defects often code for structural proteins, where one allele is sufficient to result in deficiency or malformation.
  - The disorder is usually seen in every generation on a pedigree.

- **MARFAN SYNDROME:** Connective tissue disorder.
  - **PATHOGENESIS:** Mutation in the gene for **FIBRILLIN**, which serves as a scaffold for the deposition of elastin. Fibrillin is practically gone from tissues.
  - **LOCATION:** Long arm of Chromosome 15.
  - **SYMPTOMS:** Tall and slender
    - **Arachnodactyly** = spider finger, long fingers
    - **SKELETAL:** Concave sternum
    - Hyperextensible, weak tendons and joints.
    - **CARDIOVASCULAR:** Most common cause of death.
      - Faulty media of the Aorta leads to **DISSECTING AORTIC ANEURYSMS**.
      - Heart valvulopathies.
    - **EYES:** Connective tissue problems.
      - Subluxation of lens, severe myopia, retinal detachment.

- **EHLERS DANLOS SYNDROME:** Group of connective tissue disorders.
  - **SYMPTOMS:** Hyper plasticity and fragility of skin.
    - Joint hypermobility.
    - Thin scars; bruise very easily
    - Arthritis
  - **PATHOGENESIS:** **Collagen Defect**, in some type of collagen depending on the subtype.
  - **Subtypes:**
    - **EDS I** is the most common. Normal life-expectancy
    - **EDS IV:** Type-III (Reticular) Collagen defect. Most dangerous due to potential for rupture of arteries or GI tract.
    - **EDS VII:** Type-I Collagen defect.

- **OSTEGENESIS IMPERFECTA:** Brittle bone disease.
  - **SYMPTOMS:** Group of disorders with **generalized fragility of bone, easy fractures**.
  - **PATHOGENESIS:** All subtypes involve **Type-I Collagen**.
  - **Subtypes:**
    - **OI Type I:** Normal appearance at birth, but fractures starting in infancy.
      - Only half the normal amount of Procollagen I is made.
    - **Blue Sclerae** as a consequence of deficiency of collagen fibers.
    - **OI Type II:** Fatal in utero.
    - **OI Type III:** Progressively deforming.

- **NEUROFIBROMATOSIS:** Development of Neurofibromas, benign tumors of Schwann cell origin.
  - **NEUROFIBROMATOSIS TYPE I:** Van Recklinghausen Disease. Relatively common, 1/3500 persons.
    - **PATHOGENESIS:** defect in **NF1 Gene**, which codes for a **GTPase-Activating Protein (GAP)**, involved in regulation of the **Ras** protein.
      - Normally, the NF1 gene probably suppresses Ras. Defect allows Ras to continue unabided.
  - **SYMPTOMS:**
    - **Neurofibromas** are soft pedunculated tumors. There can be many or few of them.
    - **Plexiform Neurofibromas** are large, invasive neurofibromas.
    - **NEUROFIBROSARCOMA** appears in 3%-5% of patients, usually of plexiform type.
    - **Cafe 'Au Lait Spots:** Six or more such lesions, greater than 1.5cm each in adulthood.
    - **Lisch Nodules:** Pigmented nodules of iris, which are masses of melanocytes.
    - Skeletal lesions
    - Mental Status: Mild intellectual impairment sometimes, but not retardation.
  - **NEUROFIBROMATOSIS TYPE II:** Central Neurofibromatosis. Has a separate genetic origin and is really a different disease. Chromosome 22.
    - **SYMPTOMS:** Bilateral Acoustic Neuromas.

- **ACHONDROPLASIA:** Dwarfism.
  - **PATHOGENESIS:** Inadequate endochondral bone formation.
  - **SYMPTOMS:** Short limbs, normal head and trunk, flat nose.
  o HETEROZYGOTE: Cholesterol around 250-350 mg / dL
    ▪ CHD by age 40.
  o HOMOZYGOTE: Cholesterol over 600 mg / dL
    ▪ Die of MI by age 30.
  o SYMPTOMS:
    ▪ Atherosclerosis at a very young age.
    ▪ Xanthomas: Fatty benign tumors, resulting from accumulation of fat. Nodules of lipid-laden macrophages.
• WILLIAM'S SYNDROME: Recently classified as autosomal dominant.
  o PATHOGENESIS: Absence of one of the Elastin genes.
  o SYMPTOMS:
    ▪ Characteristic facial features.
    ▪ Growth deficiency
    ▪ CARDIAC: Super valvular Aortic Stenosis, leading to a stenotic aorta. Contrast to Marfan's where you get a widened Aorta.

AUTOSOMAL RECESSIVE DISORDERS: The majority of heritable diseases are autosomal recessive.

• Heritability:
  o Rare autosomal recessive disorders often occur with consanguineous marriages.
  o Disease occurs when two heterozygotes have children -- neither parent has the disease when child gets the disease.
  o Disease shows up in one fourth of offspring of such parents.
  o Gene usually codes for a metabolic or regulatory enzyme, where one allele is sufficient to carry forth activity of the enzyme.

• CYSTIC FIBROSIS:
  o PATHOGENESIS: Defect in the CFTR (CF Transmembrane Conductance Regulator) Cl⁻ channel. It can no longer be activated by cAMP and thus never secretes Cl⁻.
    ▪ Inadequate or no excretion of Cl⁻ in glandular cells ------> little or no secretion of water ------> viscous mucous.
    ▪ Deltaf508 is the most severe mutation. Complete absence of CFTR function. There are intermediate forms.
  o SYMPTOMS:
    ▪ Chronic Pulmonary Disease ------> Bronchiectasis, widening and hypertrophy of bronchioles.
      ▪ High risk for infection.
      ▪ Most common source of morbidity and mortality
    ▪ Deficient Exocrine Pancreatic Function ------> Malabsorption
      ▪ Pancreatitis results from plugged pancreatic ducts.
    ▪ Liver: Plugged mucous in biliary system can result in biliary cirrhosis and jaundice.
    ▪ Meconium Ileus: Obstruction of the small bowel in the newborn. Caused by failure to pass meconium in neonate. Has been attributed to failure of pancreatic secretions to digest meconium.
  o DIAGNOSIS: Sweat test.
    ▪ Sweat gland cell cannot reabsorb Cl⁻ due to CFTR defect, therefore sweat is hypertonic rather than normal hypotonic.
  o EPIDEMIOLOGY: The most common lethal genetic disorder.
    ▪ Carrier state is estimated to be 1 in 25 people.

• LYSOSOMAL STORAGE DISEASES: Group of diseases in which you accumulate unmetabolized substances in lysosomes.
  o GAUCHER DISEASE: Most common storage disease.
    ▪ PATHOGENESIS: Deficiency in GLUCOCEREBROSIDASE (beta-Glucosidase) ------> accumulation of Glucosylceramide in the lysosomes of macrophages.
      ▪ GAUCHER CELLS are lipid-laden macrophages, characteristically present in spleen, liver sinusoids, lymph nodes, bone marrow.
        ▪ They have foamy cytoplasm and eccentrically located nuclei.
        ▪ Stain positive for PAS.
    ▪ SYMPTOMS / SIGNS:
- **Splenomegaly**: Virtually universal in the disease, with infiltrates of Gaucher cells in the red pulp.
- Presence of Gaucher Cells
- **EPIDEMIOLOGY**: Ashkenazi Jews principally.
- **PROGNOSIS**: They lead a normal life; usually present with Splenomegaly in adulthood.

  o **TAY-SACH'S DISEASE:**
    - **PATHOGENESIS**: Defect in beta-HEXOSAMINIDASE, resulting in failure to break down Ganglioside GM<sub>2</sub>.
    - Ganglioside: A sphingolipid, containing ceramide and N-Acetylenuraminic acid.
    - **EPIDEMIOLOGY**: Famously, Ashkenazi Jews.
    - **PATHOGENESIS**: Gangliosides accumulate in all organs, but especially in brain and retina.
    - Lipid-laden macrophages show up in gray matter of cortex in late disease.
    - **SYMPTOMS**:
      - Progressive mental deterioration
      - Blindness
      - **Cherry Red Spot** shows up on macula in funduscope. This is involvement of retinal ganglion cells.

  o **NIEMAN-PICK LIPIDOSES**: Heterogenous group of disorders relating to lysosomal storage of sphingomyelin, cholesterol, and glycolipids in macrophages, in many organs.
    - **PATHOGENESIS**:
      - **Type-I**: Defect in Sphingomyelinase
        - Sphingomyelinase hydrolyzes Sphingomyelin \(\rightarrow\) Ceramide + Phosphorylcholine
      - **Type-II**: Defect is uncertain.
      - **FOAM CELL** is characteristic: Enlarged macrophage with uniform vacuoles of lipid and cholesterol.
    - **SYMPTOMS**: BRAIN accumulation of sphingomyelin. Neurologic problems are most common cause of death. Brain atrophy.

  o **HURLER'S SYNDROME (MUCOPOLYSACCHARIDOSES)**: Accumulation of Glycosaminoglycans (GAG's) in many organs.
    - **PATHOGENESIS**:
      - Failure of any of then 10 enzymes involved in GAG breakdown.
      - GAG's: Chondroitin Sulfate, Heparin Sulfate, Keratin Sulfate.
    - Undegraded GAG's accumulate in macrophages in neurons, liver, and endothelial cells.
    - **SYMPTOMS**:
      - Death occurs in childhood, from pulmonary infections or cardiac complications.
      - Coarse facial features and dwarfism give them the nickname of **Gargoylism**.
      - CNS: Progressive gliosis and cortical atrophy.
      - SKELETAL: Deformities are a consequence of accumulation of GAG's in chondrocytes.
      - CARDIAC: Thickening and distortion of valves, chordae tendineae, and endocardium. Atherosclerosis.
      - Hepatosplenomegaly.
  - **HUNTER'S SYNDROME**: An X-Linked Mucopolysaccharidoses. Death earlier than 15 yrs of age.

  o **GLYCOGENOSES**: Glycogen storage disease.
    - **VON GIERKE'S DISEASE** (TYPE I GLYCOGENOSIS): Accumulation of glycogen in the liver.
      - **PATHOGENESIS**: Defect in GLUCOSE-6-PHOSPHATASE, such that glycogen can't be broken down in liver.
      - **SYMPTOMS**: Good prognosis with modern treatment.
        - Hepatomegaly
        - Hypoglycemia
    - **POMPE'S DISEASE** (TYPE II GLYCOGENOSIS): All organ systems involved.
      - **SYMPTOMS**: Death from heart failure by age 2.
      - **PATHOGENESIS**: Deficiency in enzyme Acid alpha-Glucosidase \(\rightarrow\) inexorable accumulation of glycogen in many different cells.
    - **MCARDLE'S DISEASE** (TYPE V GLYCOGENOSIS): Accumulation of glycogen in skeletal muscle, inability to break down muscle glycogen.
      - **PATHOGENESIS**: Deficiency in enzyme Muscle Phosphorylase, which breaks down Glycogen \(\rightarrow\) Glucose-1-Phosphate in skeletal muscle.
      - **SYMPTOMS**: Muscle cramps with exercise, possible myoglobinuria.

  • **ERRORS OF AMINO ACID METABOLISM**
o **PHENYLKETONURIA (PKU):** The leading *preventable* cause of mental retardation.
  - **PATHOGENESIS:** Deficiency in enzyme *Phenylalanine Hydroxylase*, which converts Phenylalanine to Tyrosine and also helps to break it down ---> Inability to breakdown phenylalanine.
    - Phenylalanine and its metabolites (Phenyl ketones) accumulate. It impairs development of neurons and growth of myelin in early childhood development.
    - The symptoms have been proven to originate from Phenylalanine itself.
  - **SYMPTOMS:** Progressive retardation in first few years of life, if diet is not restricted of phenylalanine.

o **ALCAPTONURIA (OCHRONOSIS):** Excretion of *Homogentisic Acid* in the urine.
  - **PATHOGENESIS:** Deficiency in *Homogentisic Acid Oxidase*.
  - **SYMPTOMS:**
    - Generalized pigmentation
    - Arthritis
    - Urine darkens rapidly upon standing.
  - **Historical Significance:** It was one of the first heritable diseases described.
  - **Ochronosis:** Referring to brown-appearing pigment of tissues.

o **ALBINISM:** Heterogenous group of disorders, all having absent or reduced biosynthesis of *Melanin*.
  - **OCULOCUTANEOUS ALBINISM:** Most common form of albinism. There are two major types.
    - **Tyrosinase-Positive OCA:** Most common form.
      - Complete Albinism early on, but some pigment accumulates later.
      - **PATHOGENESIS:** Basic biochemical defect is not known.
    - **Tyrosinase-Negative OCA:** Complete absence of Tyrosinase and therefore melanin.
      - **SYMPTOMS:**
        - Snow-white hair, pink eyes, pink skin
        - Severe Ophthalmic Problems: Photophobia, decreased visual acuity, nystagmus, strabismus

• **SMITH-LEMLI-OPITZ SYNDROME:** No blood cholesterol.
  - **PATHOGENESIS:** Defective enzyme in the cholesterol synthesis pathway.
    - *Virtually no endogenous cholesterol.*
    - Buildup of 7-Dehydrocholesterol due to blocked biosynthesis pathway.
  - **SYMPTOMS:** Death at age of six weeks.
    - Some polydactyly and syndactyly
    - Club foot
    - Heart defects

X-LINKED DOMINANT TRAITS: Very rare.

- Females would be affected twice as often as males.
- **Familial Hypophosphatemia (Rickets)**
- **Ornithine Transcarbamylase Deficiency:**
  - **SYMPTOMS:**
    - Babies will have very high ammonia levels in newborn period.

X-LINKED RECESSIVE:

• **DUCHENNE/BECKER MUSCULAR DYSTROPHY:** Severe muscle-wasting disease.
  - **PATHOGENESIS:** Deficiency of enzyme *Dystrophin*, a membrane cytoskeletal protein, like spectrin, found in muscle.
    - Dystrophin molecules form an intracellular network (anchored to cytoplasm), important in forming mechanical properties of muscle.
    - **FLEXIBILITY is lacking MD.**
  - **SYMPTOMS:** Death by 17 years
    - Failure to walk by 18 months
    - **Pseudohypertrophy** of calf muscles.
    - Progressive retardation.
    - Cardiac problems (frequent cause of death)
• **HEMOPHILIA-A** (FACTOR VIII DEFICIENCY): No clotting; spontaneous bleeding into joints, muscles, internal organs.
  - PATHOGENESIS: The Factor VIII gene is very large.
  - SYMPTOMS: Deforming arthritis is common complication, caused by bleeding into joints.
  - TREATMENT: Recombinant Factor VIII

• **FRAGILE-X SYNDROME:**
  - PATHOGENESIS: Expansion of trinucleotide repeats on the X chromosome. The more the repeats, the greater the level of retardation.
    - Inheritance tends to amplify the number of repeats.
    - CGG is the repeated triplet in Fragile X syndrome.
  - SYMPTOMS: Second only to Down's Syndrome as a cause of mental retardation.
    - Frequently seen with Autism as well as mental retardation.

MULTIFACTORIAL DISEASES: Multiple genes and environmental factors.

• Heritability:
  - Probability of affecting later offspring is affected by whether older siblings are affected.
  - The more severe the defect, the greater the risk of transmission.
  - The expression of symptoms is proportional to the number of mutant genes.

• **CLEFT LIP and CLEFT PALATE:** Failure of closure of frontal prominence with maxillary process, either unilaterally or bilaterally.
  - PATHOGENESIS: Multifactorial inheritance. Multiple genes direct it, and environmental factors at the time can influence it.
    - Having one Cleft-Lip baby

• Common examples of adult diseases
  - HYPERTENSION
  - DIABETES TYPE II
  - PSORIASIS
  - SCHIZOPHRENIA
  - ATHROSCLEROSIS
  - GOUT
  - ANKYLOSING SPONDYLITIS

• Common Examples of Childhood Diseases:
  - CONGENITAL HEART DISEASE
  - PYLORIC STENOSIS

Diseases of Infancy and Childhood:

• **PREMATURE BIRTH:**
  - **Appropriate for Gestational Age (AGA):** Premature Birth
    - Risk Factors:
      - Maternal Illness
      - Uterine Incompetence
      - Fetal Disorders
      - Placental Abnormalities
    - SYMPTOMS: IRDS, metabolic disturbances (jaundice), anemia, bacterial sepsis
  - **Small for Gestational Age (SGA):** *Low Birth-Weight Babies*
    - Risk Factors
      - Impaired maternal health and nutrition
      - Interference with placental circulation or function
      - Disturb the growth or development of the fetus.
    - SYMPTOMS: Much more heterogeneous. Congenital birth defects.

• **PREMATURE ORGANS:**
  - LUNGS: *Amniotic Fluid Aspiration* is actually retained amniotic fluid (it never evacuates the lungs) in premature infants.
  - LIVER: Premature infant is deficient in *Glucuronyl Transferase*, which results in accumulated bilirubin --> *Neonatal Jaundice*.
  - BRAIN: Incomplete CNS development at birth.
INFANT RESPIRATORY DISTRESS (IRDS): Premature infants have no Pulmonary Surfactant at birth, leading to infant Hyaline Membrane Disease, or atelectasis of the alveoli.

- SYMPTOMS: HYPOXIA -----> Pulmonary Vasoconstriction -----> Increased Right to Left shunting through Foramen Ovale and Ductus Arteriosus
  - Cyanosis

ERYTHROBLASTOSIS FETALIS:

- PATHOGENESIS: Most commonly, an Rh- sensitized mother giving birth to her second Rh+ child. Rh+ child will then elicit antibodies from maternal circulation -----> massive fetal anemia.
  - There are other more minor form of erythroblastosis, involving other antigenic incompatibilities.

- SYMPTOMS:
  - HYDROPS FETALIS: Severe edema and secondary congestive heart failure in fetus, caused by severe anemia. Fatal.
  - KERNICTERUS: Bilirubin Encephalopathy results from fetal jaundice. Bilirubin staining of brain, particular pontine nuclei, basal ganglia, dentate nucleus.
    - Any infant with jaundice is susceptible to Kernicterus

BIRTH INJURY:

- CEPHALOHEMATOMA: Subperiosteal hemorrhage defined to a single cranial bone.
  - SYMPTOMS: They usually resolve without complications.
- INTRACRANIAL HEMORRHAGES: May lead to Cerebral Palsy. Can result from traumatic delivery.

SUDDEN INFANT DEATH SYNDROME (SIDS): Leading cause of death during first year of life.

- PATHOGENESIS: Unknown, although sleep apnea may play a role.
- RISK-FACTORS: Sleeping in prone position, smoking parents, socioeconomic status

NEOPLASMS OF INFANCY and CHILDHOOD:

- HAMARTOMAS: Focal, benign overgrowths of one or more of the mature cellular elements of normal tissue.
- HEMANGIOMAS: Either a hamartoma or a true neoplasm.
  - PORT WINE STAIN: Dark purple color to affected area, capillary hemangioma, like a bruise.
  - They may regress spontaneously.
- LYMPHANGIOMAS: Cystic Hygromas
  - MORPHOLOGY: Unilocular or multilocular cysts along lymphs vessels in head and neck region.
  - They do not regress spontaneously and should be resected.
- SACROCOCCYGEAL TERATOMAS: Germ cell neoplasm, the most common solid tumor in the newborn.

HEMODYNAMIC

HEMORRHAGE:

- PURPURA: Diffuse superficial hemorrhage, up to 1cm in diameter.
- ECCHYMOSIS: Bruise.
- PETECHIA: Pinpoint hemorrhage, esp. in conjunctivae and skin.

HYPEREMIA

- PHYSIOLOGIC (ACTIVE): Exercise
- PASSIVE: Congestive
  - Lung: Heart Failure Cells have hemosiderin.
  - Liver: Nutmeg Liver
  - Spleen
  - Edema and Ascites
THROMBOSIS: Clot. Technically a thrombus is adherent to vascular endothelium.

- **LINES OF ZAHN**: Help distinguish a thrombus from a post-mortem clot which is where blood coagulates post-mortem and separates into layers.

EMBOLISM: Anything that knocks loose and lodges in the blood.

- **AIR EMBOLUS**: As in Decompression Disease
- **AMNIOTIC FLUID EMBOLUS**: Can lead to Disseminated Intravascular Coagulopathy (DIC), due to the presence of Thromboplastin in amniotic fluid.
- **BONE MARROW EMBOLUS**
- **FAT EMBOLUS**: Large bone fractures
- **FOREIGN BODY EMBOLUS**: Bullet
- **PARADOXICAL EMBOLUS**: Emboli originally from venous side go to arterial side and cause an infarct, due to a patent foramen ovale or other septal defect.
- **THROMBO EMBOLUS**: Most common.

ANASARCA: Profound, generalized edema.

DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC): Usually fatal. Thousands of intravascular micro-clots which consume all platelets and result, paradoxically, in uncontrolled bleeding in certain areas.

- **CAUSES**:
  - Amniotic Fluid Embolus, release of Thromboplastin into blood.
  - Gram negative endotoxic shock

TROUSSEAU SYNDROME: Paraneoplastic syndrome of hypercoagulable state. Classically associated with pancreatic cancer

INFARCTION: Acutely, it leads to Coagulative Necrosis.

- **RED INFARCT**: Pulmonary infarct, or infarct of an organ that has dual blood supply.
- **PALE INFARCT**: Single blood supply, as in kidney.

EDEMA: OK?

SHOCK:

- **CARDIOGENIC SHOCK**
- **SEPTIC SHOCK**
- **TOXIC SHOCK**: Due to Staph and Strep exotoxin, TSS. These bugs are induced to make TSS by the presence of a rare phage.
- **HYPOVOLEMIC SHOCK**
- **NEUROGENIC SHOCK**: ANS failure.
- **STAGES**:
  - REVERSIBLE: High vasoconstriction, vascular tone.
  - CRITICAL: Very high TPR
  - IRREVERSIBLE: Pooling and stagnation, interstitial edema, severe acidosis.