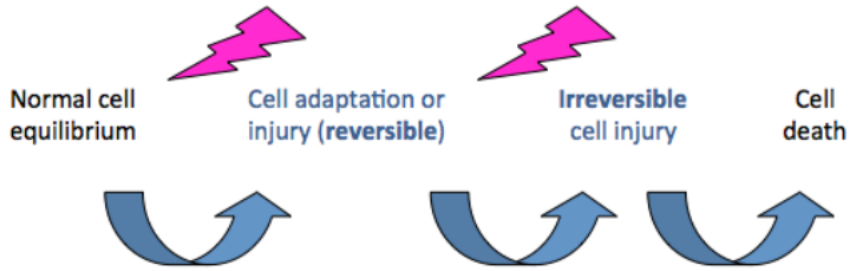
PATHOLOGY I
BLOCK 1

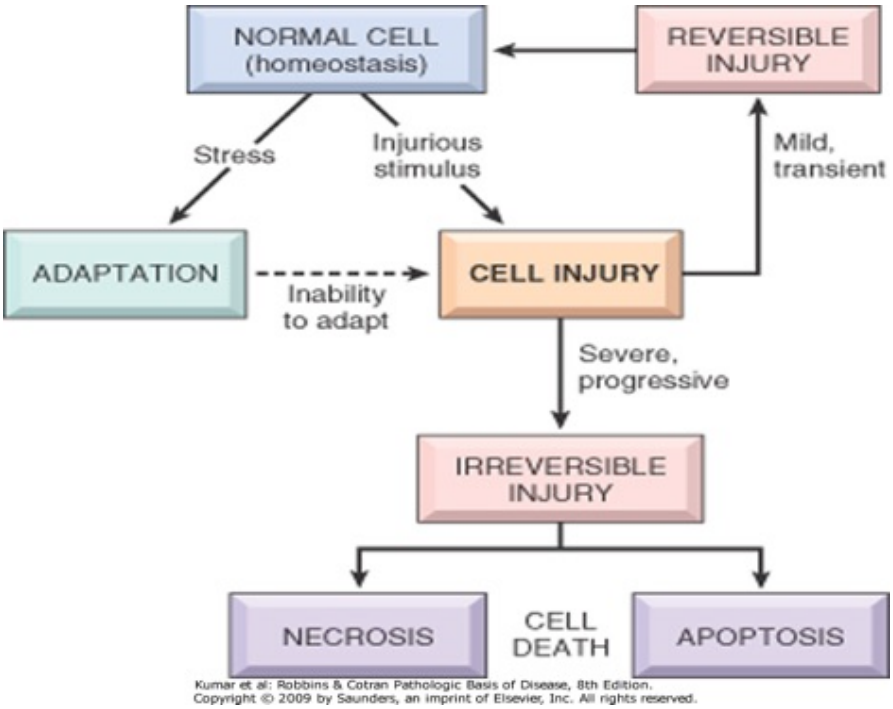
Brad Trent

Resources Used: Dr. Jiji's Lecture Slides, Pathoma, Rubins, Robbins, TA Slides

ADAPTATION



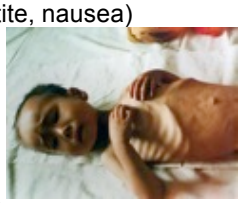
- When stress is added to cell in normal state of equilibrium, the cells **adapt** to maintain function.
- With increased or prolonged stress, the cells become **injured**, but still partially maintain function.
  - Sometimes after stress is removed, the cells may be able to ***reverse*** the injury & revert back to normal equilibrium.
- Other times, increased or prolonged stress causes the cells to become **injured** beyond the **point of no return**: ***Irreversible*** *injury*
  - *The stress on the cell has to push it past a point of no return to be irreversible, which eventually leads to cell death.*
  - *A common example is dysplasia versus carcinoma in situ – Dysplastic cells are still reversible, whereas CIS is not*
- *The key to remember with any cell adaptation and/or cell injury is the ability (or inability) of the cells to adapt to maintain function & the duration/severity of the increased or prolonged stress. This will determine whether the injury is reversible or irreversible – If the cell cannot adapt, it will experience injury!*



TYPES OF ADAPTATIONS: Atrophy, Hypertrophy, Hyperplasia, Metaplasia/Dysplasia, Accumulation/Deposition

1. ATROPHY*: *Decrease in stress → decrease in size*

- Loss of quantity, size, and/or volume of cell mass with consequent decrease in function
- CAUSES OF ATROPHY/ETIOLOGY:
  - Reduced functional demand/Disuse – *when you stop using a muscle; i.e. after in a cast* – reversible
  - Denervation – *most muscles require nervous stimulation, so if you cut that nerve, you'll get atrophy of the muscle; i.e. concavity of thenar muscle (carpal tunnel)*
  - Malnourishment/starvation – *musculature & non-vital organs atrophy significantly*
    - **Marasmus**: protein + caloric deficiency; muscle-wasting
    - **Cachexia**: wasting that can't be reversed nutritionally (often in **cancer**)
      - Pathophysiology – cancer "steals" resources at expense of body, side effects of cancer (decreased appetite, nausea)



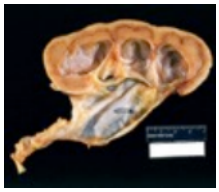
    - **Kwashiorkor**: protein deficiency; distended abdomen
  - Loss of endocrine stimulation/hormonal withdrawal – *i.e. PMB example below*
  - Persistent injury
  - Progressive loss of blood supply (aging, pressure) – *results in decreased nutrients*
- *Adaptive response of controlled cell growth that is **REVERSIBLE***

ATROPHY EXAMPLE: ENDOMETRIAL BIOPSY – PMB

- To evaluate abnormal menstrual bleeding (r/o pre-cancer or cancer)
- **Menorrhagia**: excessive bleeding
- **Menometrorrhagia**: excessive & irregular bleeding
- **PMB**: post-menopausal bleeding
- *31 y/o female with menometrorrhagia:* Microscopically normal
- *61 y/o female with PMB:* Atrophy due to hormonal withdrawal

ATROPHY EXAMPLE: UNILATERAL HYDRONEPHROSIS

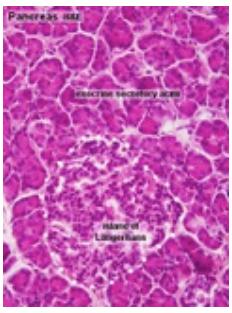
- Renal atrophy due to obstruction or blockage of the ureter
- **PRESSURE ATROPHY**



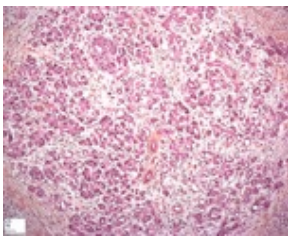
ATROPHY EXAMPLE: CHRONIC PANCREATITIS

- Gallstones & alcoholism are the top 2 causes of chronic pancreatitis
- The point of the slide in the notes is that this is illustration of chronic inflammation/injury that contributes to atrophy of those cells. If the pancreas gets inflamed, pancreatic enzymes are secreted in the pancreas, NOT where they belong → CHRONIC INJURY

Normal Pancreas

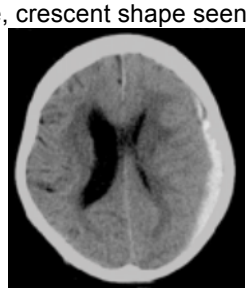


Chronic Pancreatitis

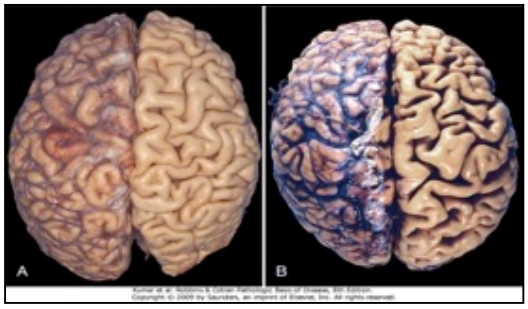


ATROPHY EXAMPLE: SUBDURAL HEMATOMA

- *76 y/o male brought by family with confusion & disorientation; history of a-fib; fell at home 8 hours ago with no immediate symptoms following fall. PE: no localizing neurological defect, but he showed lack of orientation to time & place; order head CT*
  - KEY POINTS: age, risk of thrombosis due to a-fib, fell at home (not traumatic MVA), seemingly normal until onset of symptoms 8 hours later
  - Compression of L lateral ventricle, crescent shape seen indicating subdural hematoma



- PATHOGENESIS: aging & atherosclerosis → vascular occlusion → progressive ischemia, reduced delivery of oxygen/nutrients, **atrophy** (loss of brain tissue mass), retraction from inner skull surface causes stretching of veins bridging from dural venous sinuses to brain (now vulnerable to hemorrhage)
- PATIENT FALLS: sudden traumatic movement tears veins → hemorrhage (venous) into subdural space



A: normal brain of a young adult; **B**: atrophy of brain in an elderly male with atherosclerotic cerebrovascular disease resulting in reduced blood supply. **NOTE:** Loss of brain substance/atrophy narrows the gyri & widens the sulci

TWO TASKS INHERENT TO ATROPHY:

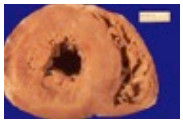
1. Halt cell proliferation – suppress growth factors
2. Degrade existing cells via **ubiquitin-proteasome pathway (**organized way for cell to tag proteins destined for degradation)
3. *According to Pathoma, atrophy occurs due to a decrease in cell number or decrease in cell size. A decrease in cell number occurs via apoptosis. A decrease in cell size occurs via ubiquitin-proteasome pathway & autophagy.*

DO NOT CONFUSE ATROPHY WITH...

- **Agenesis/*Aplasia***: failure to form/develop at all during embryogenesis; i.e. unilateral renal agenesis
- **Hypoplasia**: (congenital) incomplete development; *decrease in cell production during embryogenesis, resulting in a relatively small organ* i.e. pulmonary hypoplasia
- **Atresia**: failure to form tubular structure or opening; i.e. esophageal/intestinal atresia, biliary atresia, etc.
  **These phenomena imply faulty origin & were not previously normal – Atrophic tissues were once normal!*

2. HYPERTROPHY*: *Increase in stress → increase in organ size*

- Increase in SIZE of cells (& eventually tissues), generally results in increased functional capacity
- *Involves gene activation, protein synthesis, & production of new organelles*
- Etiology: increased functional demand or hormonal effects
- *Hypertrophy is an adaptive response that is still controlled cell growth & is **REVERSIBLE***
- **Physiological Hypertrophy**
  - Adaptive mechanisms that occurs in **PERMANENT CELLS** like neurons, cardiac muscle, & skeletal muscle **without hyperplasia**
  - Uses the PI_3K/AKT/PKB pathway (exercise-induced)
  - Example: *skeletal muscle in exercise*
    - Endurance: increased # & volume of mitochondria → increased cell SIZE
    - Resistance: enlarged contractile elements & increased capillary network → increased cell SIZE
  - Uterine myometrium during pregnancy
- **Pathological Hypertrophy**
  - Responds to increased functional demand by using various G-protein pathways that are stimulated by GFs (TGF-β, IGF-1, α-adrenergics)
  - Example: *myocardial (left ventricular) hypertrophy due to chronic HTN***
    - Switch from adult alpha heavy chain myosin to fetal beta heavy chain myosin because the fetal form is more energetically economical
    - Genes for ANF are re-expressed: ANF → increased salt loss from kidney → decreased blood volume & pressure



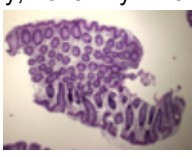
  - Example: *acromegaly due to excess secretion of growth hormone from pituitary adenoma*
    - Excess GH leads to increase in soft tissue

3. HYPERPLASIA*: *Increase in stress → increase in organ size*

- Increase in NUMBER of cells & production of new cells **from stem cells** due to increased functional demand, hormonal effects, persistent cell injury that occurs in **non-permanent cells** that can undergo division
  - Permanent tissues (cardiac/skeletal muscle, neurons) don't have stem cells → can't undergo hyperplasia
- Like hypertrophy, hyperplasia can be an adaptive physiological response or an injurious pathological response
- **Physiological Hyperplasia***
  - Hormonal hyperplasia during **breast development** at puberty or during **pregnancy**
  - Compensatory hyperplasia where liver regrows after a portion is resected
- **Pathological Hyperplasia**
  - Parathyroid hyperplasia due to primary or secondary **hyperparathyroidism**
    - Patient with *renal dysfunction* presents with significant problems due to excessive PTH & hypercalcemia
  - Endometrial hyperplasia due to excessive estrogen secretion

HYPERPLASTIC EXAMPLE: COLON POLYP

- 50 y/o M presents for colonoscopy; no family hx of colon cancer; one 4 mm polyp is found in sigmoid colon

Normal →  **Abnormal →** 

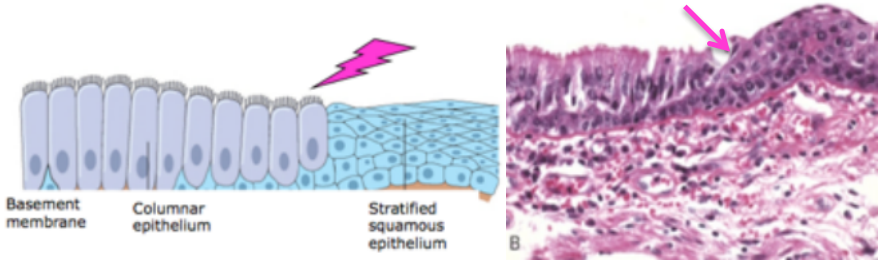
HYPERTROPHY	HYPERPLASIA
Increase in CELL SIZE	Increase in CELL NUMBER
Cellular changes: Cytoplasm increased More ribosomes → protein Nucleolus enlarged Nucleus enlarged but less basophilic (chromatin dispersed) Increased DNA transcription	**NOTE: PERMANENT TISSUES (CARDIAC MUSCLE, SKELETAL MUSCLE, & NERVES) CANNOT UNDERGO HYPERPLASIA, AS THEY DO NOT HAVE STEM CELLS!!!!!!!!**
Both may lead to increase in tissue mass (i.e. size of the organ) Both also lead to increase in functional capacity (adaptive) or disease (maladaptive/pathologic)	

4. METAPLASIA*: *Change in stress → change in cell type*

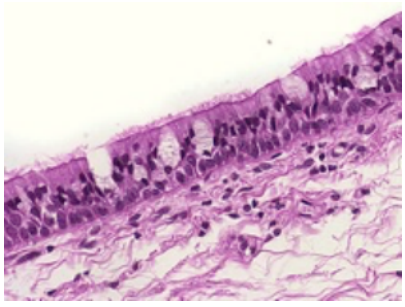
- Adaptive change from one differentiated cell type to another
  - NOT a change of the differentiated cells themselves, BUT rather a change from the *stem cells* of origin
- *Most commonly involves change of surface epithelium (squamous, columnar, or urothelial/transitional)*
- *Adaptive response of controlled cell growth that is **REVERSIBLE***

METAPLASIA EXAMPLE: SQUAMOUS METAPLASIA*

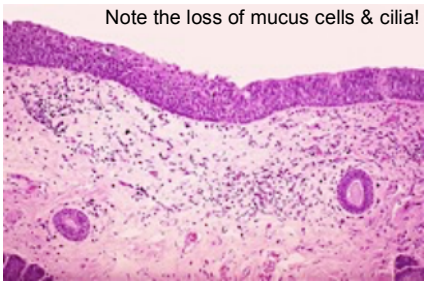
- ***Squamous metaplasia is the transformation of differentiated epithelium to stratified squamous epithelium***
- i.e. pseudostratified columnar epithelium **into squamous epithelium** in bronchi of smokers
  - In the bronchi, this is a *protective mechanism* in response to chronic irritation from toxins in cigarette smoke
  - There is decreased cilia & mucus production
  - Malignant transformation may occur
- i.e. transitional epithelium of the bladder → squamous epithelium due to irritation from bladder stones
- i.e. epithelium lining ducts of exocrine glands (salivary, pancrease, bile ducts) irritated with calculi → squamous
- Can be associated with **Vitamin A (Retinoic Acid) Deficiency** affecting conjunctiva covering the eye



Normal bronchi →

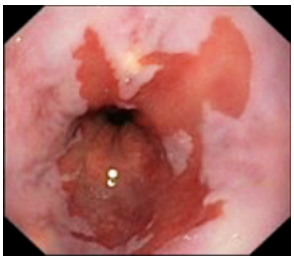


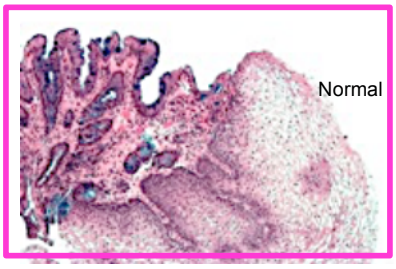
Abnormal bronchi →



METAPLASIA EXAMPLE: BARRETT'S ESOPHAGUS – *Specialized Intestinal Metaplasia*

- *73 y/o male with hx of recurrent epigastric pain/GERD has EGD with the following findings: salmon-pink 'tongues' of discoloration at gastro-esophageal junction extending proximally into esophagus; biopsy performed*
- *The histological slide (seen on the right) is NOT of the **anatomical** junction; it only shows the TRANSITION from one type of epithelium to another, where a transition occurs that is NOT NORMALLY PRESENT – METAPLASIA*





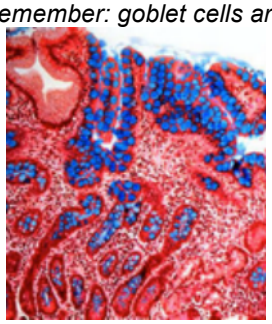
- Chronic GERD causes normal non-keratinized **squamous epithelium of the esophagus** to change to columnar epithelium & then **to columnar epithelium with goblet cells** (*mucin-filled cells, stained blue with mucin stain*), an **adaptive mechanism to withstand stomach acid coming into esophagus from stomach**
  - You do not normally find goblet cells in stomach or esophagus
  - You would expect to see goblet cells once entering duodenum, as their role is to neutralize gastric acid
- **Clinical significance**: increased esophageal cancer risk
- Surveillance endoscopies are performed to look for DYSPLASIA. Metaplasias can progress to dysplasia & eventually result in cancer.
- ***NOTE**: when looking at histological slides, the basement membrane is very difficult to see.*

TRANSITION ZONES

- **Uterine cervix**: squamous to glandular epithelium
- **Esophagus to stomach**: stratified squamous epithelium of esophagus to simple columnar epithelium of the stomach **This is important to know – Barrett's esophagus is high yield!*
- **Oropharynx to nasopharynx**: non-keratinized stratified squamous epithelium of oropharynx to pseudostratified ciliated columnar epithelium of the nasopharynx
- **Anus to rectum**: simple epithelium of rectum to stratified squamous epithelium of anal canal

METAPLASIAS

- **Intestinal metaplasia of stomach – atrophic gastritis**
  - Intestinal-type epithelium with numerous goblet cells (stained blue) replacing the gastric mucosa & representing gastric atrophy – *Remember: goblet cells are not normally found in the stomach*

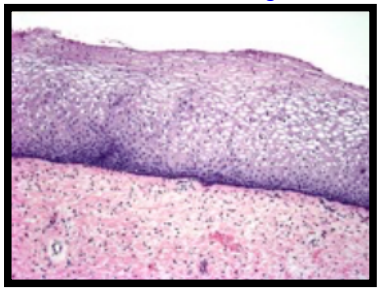


- Intestinal metaplasia of gallbladder
- Squamous metaplasia in endocervical canal – polyp (benign)
  - Irritative metaplasia, but no clinical consequences seen
- Squamous metaplasia of bladder
  - Transitional epithelium of the bladder → squamous epithelium due to irritation from bladder stones
- Squamous metaplasia of prostate
- Pancreatic acinar metaplasia of GEJ

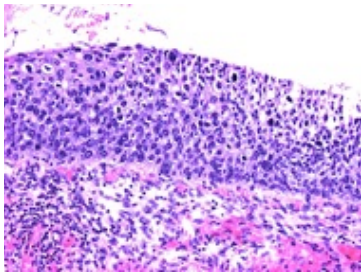
4b. DYSPLASIA*

- Morphologically recognized alteration in size, shape, & arrangement of cells that signifies a propensity to develop neoplasia (*the pathological process resulting in abnormal growth of cells*)
- Morphologic changes are indicative of pathology **at the DNA level**
- Usually due to chronic irritation & longstanding hyperplasia/metaplasia
- Dysplasia is an "early form" of neoplasia
- *Disordered & uncontrollable cellular growth that IS STILL **REVERSIBLE***

Normal →

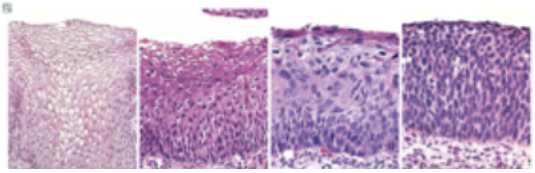


Severe dysplasia→



Robbins Pgs. 1002-1004: Cervical Dysplasia & Neoplasia

- Squamous metaplasia/mild chronic inflammation on pap smear is not concerning
- Low-grade squamous intraepithelial lesion (LSIL) is associated with a productive HPV infection, but does not progress directly to invasive carcinoma & most cases regress spontaneously
- In high-grade squamous intraepithelial lesion (HSIL) there is a progressive deregulation of the cell cycle by HPV, which may become irreversible and lead to a fully transformed malignant phenotype. Thus, all HSILs are considered to be at high risk for progression to carcinoma.

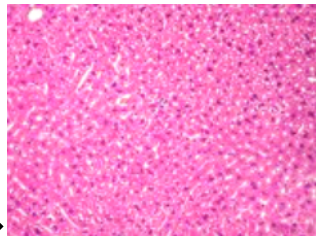


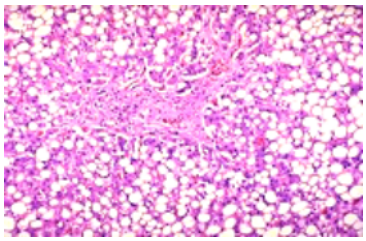
5. INTRACELLULAR ACCUMULATIONS/DEPOSITIONS

- Can be an adaptive mechanism OR cell injury
- Intracellular storage which becomes exaggerated

ACCUMULATIONS EXAMPLE: STEATOSIS

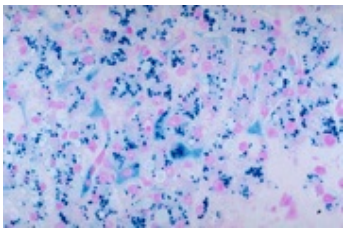
- Abnormal retention of lipids within a cell due to dysfunctional synthesis and/or elimination of TGs
- "Fatty liver" – portal triad seen in the middle; large vacuoles/accumulations of lipids are seen
- *COMMON IN **ALCOHOLICS***

Normal liver → 

Steatosis → 

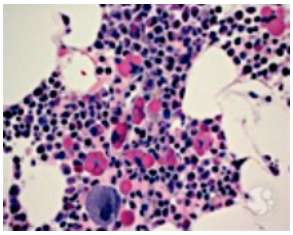
ACCUMULATION EXAMPLE: HEMOSIDEROSIS

- Iron overload disorder causing abnormal accumulations of hemosiderin seen in areas of HIGH RBC TURNOVER or RECENT HEMORRHAGE
- Often seen in patients who are getting a lot of **BLOOD TRANSFUSIONS**
- Macrophages have phagocytized the dead RBCs
- ***Liver, LUNGS, spleen, kidneys, lymph nodes, & bone marrow
- PRUSSIAN BLUE STAIN FOR HEMOSIDEROSIS



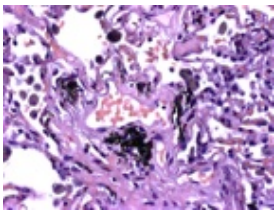
ACCUMULATION EXAMPLE: (MULTIPLE MYELOMA, possibly)

- Abnormal accumulation of protein in the form of antibodies
- *"Russell bodies" – accumulation of immunoglobulins in plasma cells*



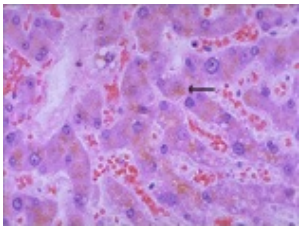
DEPOSITION EXAMPLE: ANTHRACOSIS

- "Coal workers lung"
- Carbon deposits in lung tissue
- *Anthratic pigments from dust particles inhaled over years*



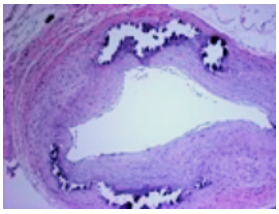
DEPOSITION EXAMPLE: LIPOFUSION

- "**AGE PIGMENT**" – *BROWN PERINUCLEAR PIGMENT*
- Due to **free radical peroxidation** of membrane lipids commonly seen in **CARDIAC MYTOCYTES** & hepatocytes

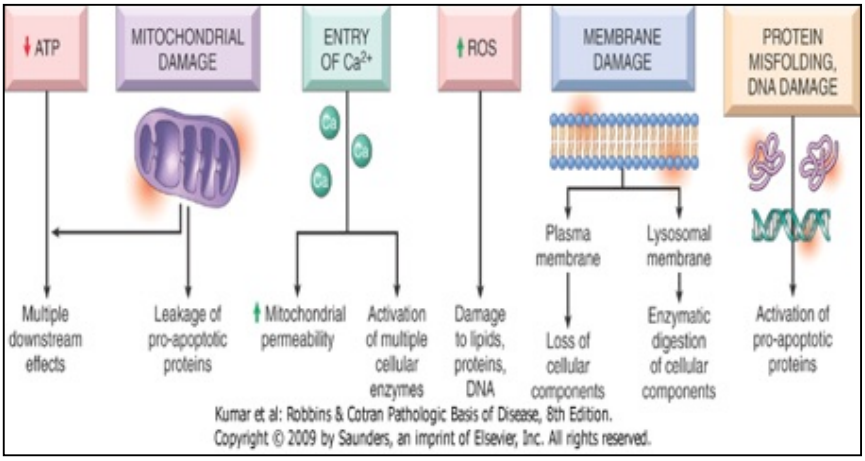


DEPOSITION OF CALCIUM IN VASCULAR WALLS

- Change that is expected to see in elderly



CELL INJURY



KEY DRIVERS OF CELL INJURY:

1. Loss of ATP
2. Increase in cytoplasmic Ca^{2+}
3. Generation of reactive oxygen species (ROS)

ISCHEMIA: lack of perfusion of tissues or *poor venous drainage*/blockage of blood flow that USUALLY leads to hypoxia;

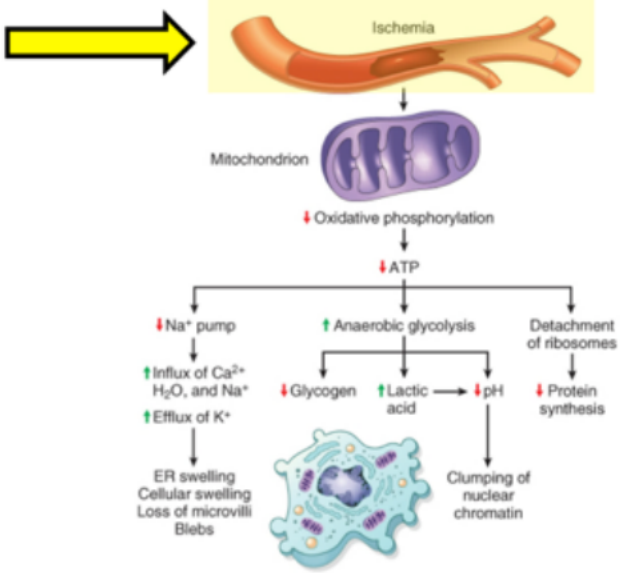
- **Ischemia without hypoxia**: collateral circulation, pulmonary infarct, endocardial preservation in MI
- *Common causes of ischemia: decreased arterial perfusion (atherosclerosis), decreased venous drainage, shock*

HYPOXIA: low O_2 delivery to the tissues, which *impairs oxidative phosphorylation*; it is most commonly caused by ischemia or hypoxemia; BUT you can have hypoxia WITHOUT ischemia!

- **Hypoxia without ischemia**: decreased O_2 in ambient air (altitude), decreased ventilation (less air being brought into the lungs), decreased O_2 transfer in lungs (emphysema), decreased O_2 carrying capacity of blood (anemia, Hb defect), competition for O_2 binding sites in blood (carbon monoxide poisoning)

1. LOSS OF ATP

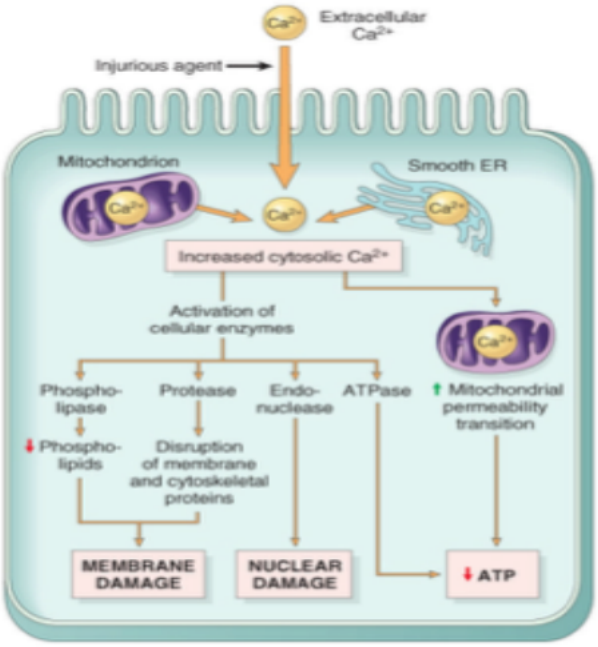
- **Ischemia** causes less O_2 to be delivered to tissues (HYPOXIA), which severely impairs oxidative phosphorylation
- Loss of function of the Na^+/K^+ ATPase pump → Na^+ is not pumped out causing constant depolarization of the cell & opening of Ca^{2+} channels for Ca^{2+} influx
- Increased demand for anaerobic glycolysis causes increased lactic acid & decreased intracellular pH resulting in clumping of chromatin
- Decreased protein synthesis due to ribosomal dysfunction & swelling
- *Cell swelling, cytoplasmic eosinophilia, ribosome swelling, blebbing, altered cytoskeleton*



***KNOW THIS IMAGE!**
The morphological changes shown here are indicative of reversible cell injury. Further depletion of ATP results in cell death, typically by necrosis.

2. INCREASED CYTOPLASMIC Ca^{2+}

- Normal Ca^{2+} homeostasis: 1.3 µmol ECM vs 0.1 µmol ICM
- Increased Ca^{2+} activates phospholipase, protease, endonuclease, ATPase, etc. leading to adverse effects within the cell – *can lead to irreversible cell injury*
  - Lipid peroxidation and membrane damage
  - Increased mitochondrial permeability causes the release of cytC (which sets off apoptosis)
  - Increased ROS
- Increased Ca^{2+} activates mitochondrial permeability transition pore, which when opened results in the loss of membrane potential of mitochondria, further limiting oxidative phosphorylation (and less ATP means more Ca^{2+} influx → vicious cycle)



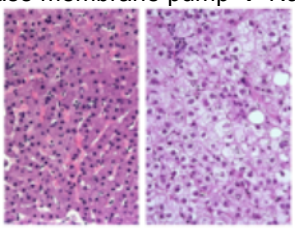
3. GENERATION OF REACTIVE OXYGEN SPECIES

- ROS are produced from normal by-product of redox reactions, enzymatic metabolism of drugs & chemicals, radiation, metals (**IRON**, COPPER), inflammatory cells, nitric oxide
- ROS are removed by spontaneous decay, enzymes (superoxide dismutase, catalase, **glutathione peroxidase**), antioxidants (Vitamin A, C, **E**), binding proteins (transferrin, ferritin – Fe binding; & ceruloplasmin – Cu binding)
- **Pathological effects of ROS production:**
  - Lipid peroxidation → membrane damage
  - Protein modification → breakdown, misfolding
  - DNA damage → mutations

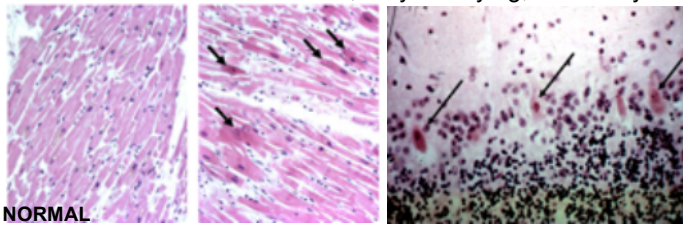
*KNOW THIS TABLE!		
$O_2^{\cdot -}$	Superoxide anion	Increased production of degradative enzymes Damages lipids, proteins, DNA
H_2O_2	Hydrogen peroxide	Intermediary (precursor to $^{\cdot}OH$) Can act distant from site of production
$^{\cdot}OH$	Hydroxyl radical	Most potent ROS Primary ROS causing damage to lipids, proteins, DNA
$ONOO^-$	Peroxynitrite	Damages lipids, proteins, DNA

MORPHOLOGICAL SPECTRUM OF REVERSIBLE CELL INJURY

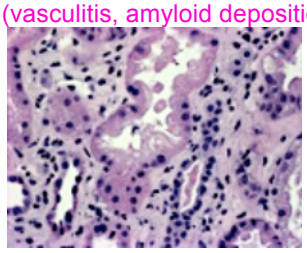
- Increased intracellular volume (**cell swelling**)
  - Reduced activity of Na^+K^+ ATPase membrane pump → Na^+& water accumulate in cytoplasm



- Cytoplasmic eosinophilia
  - General increase in the ability of those cells to bind to eosin stain → increased redness of the cell
  - ***Acidification, Ca^{2+}-activating enzymes, mitochondrial damage***
  - The image on the left is nearly normal myocardium with no morphological changes of injury
  - The image in the middle shows cells (arrows) with much more red – consequence of early phases of injury due to acidification from increase in lactic acid in cells, activation of enzymes breaking down cytoskeleton
  - The image on the right shows the granular layer of the cerebellum – the arrows are pointing at neurons
    - "Dead reds" – when neurons turn red, they are dying; extremely suspicious of hypoxia



- Plasma membrane **blebbing** (protrusions)
  - Lipid/phospholipid & cytoskeletal damage by Ca^{2+}-activated enzymes & ROS
  - Image shows the **renal cortex**
    - **There are 4 histological components that are important for a renal biopsy:** glomeruli, tubules, blood vessels (vasculitis, amyloid deposition), & interstitium (interstitial nephritis)



- Chromatin clumping & redistribution due to decreased pH

FUNCTIONAL CONSEQUENCES OF INJURY

- Shift to glycolytic pathway to generate ATP
- Accumulation of lactic acid and inorganic P
- Lack of ATP, decreased pH, mitochondrial dysfunction, ionic imbalance – all impair cell function
- Function loss & consequences thereof depends on cell type & role

According to pathoma,

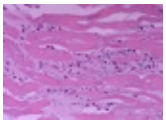
- *The initial phase of injury is **reversible***. The hallmark of reversible injury is **cellular swelling**.*
  - *Cytosol swelling results in loss of microvilli & membrane blebbing.*
  - *Swelling of the RER results in dissociation of ribosomes & decreased protein synthesis.*
- *Eventually, the damage becomes **irreversible***. Irreversible injury starts off with severe **membrane damage**.*
  - *Plasma membrane damage results in cytosolic enzymes leaking into the serum (i.e. troponin) & additional calcium entering the cell.*
  - *Mitochondrial membrane damage results in the loss of ETC (inner mt membrane) & cytC leaking into cytosol & initiation apoptosis.*
  - *Lysosomal membrane damage results in hydrolytic enzymes leaking into the cytosol, which, in turn, are activated by the high intracellular calcium.*

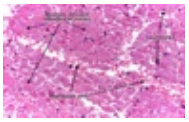
IRREVERSIBLE CELL INJURY & DEATH

*The morphologic hallmark of **cell death** is **loss of the nucleus**. 2 mechanisms of cell death: necrosis & apoptosis.*

NECROSIS: *aka "murder"; the sum of the morphological changes indicative of cell death & caused by the progressive degradative action of enzymes; it affect usually affects **groups of cells***; followed by **inflammation**

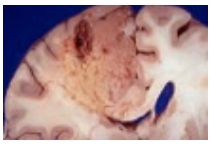
1. Coagulative necrosis: *necrosis in which tissue becomes a dry, opaque, eosinophilic mass containing the outlines of anucleated cells, resulting from the **denaturation of proteins** following hypoxia, such as that caused by ischemia in infarction*



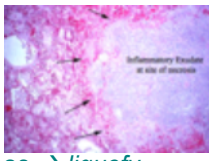


- Due to ischemia/hypoxia of all tissues **EXCEPT THE BRAIN**
- MAINTAINS STRUCTURE *via coagulation of proteins*
- Forms firm tissue due to coagulation of **denatured cellular proteins**
- **CLASSIC EXAMPLE – MI** (pic) or pulmonary infarct from embolus/ thrombosis
  - ***Vascular occlusion** – "wedge shape"*

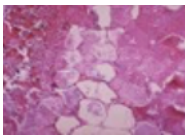
2. Liquefactive necrosis: *necrosis in which the necrotic tissue becomes soft & liquefied due to enzymatic lysis of cells*



- Loss of structure due to enzymatic digestion
- Two general scenarios:
  - **BRAIN – CEREBRAL INFARCT** rapidly followed by enzymatic digestion of microglial cells, resulting in space filled with viscous liquid
  - **Not in brain** – often infectious cause
    - Rate of cell death > rate of repair/resolution
    - Result of massive dump of enzymes released by infiltrating inflammatory cells
    - **CLASSIC EXAMPLE – ABSCESS** (right): circumscribed collection of dead cells/debris & inflammatory cells (**neutrophils**) – "inflammatory exudate"
      - Host response employed to contain/destroy an injurious agent
      - Abscesses are localized, circumscribed, & well-demarcated
    - ***PANCREATITIS** – proteolytic enzymes activated within pancreas digest the pancreas → liquefy*

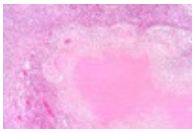


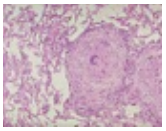
3. Fat necrosis: *fats in the cells of adipose tissue are split by enzymatic action into fatty acids & glycerol, producing chalky white areas where the released FAs react with Ca, Mg, & Na ions (saponification); aka steatonecrosis*



- **ALCOHOLICS**
- Death of adipocytes leads to large efflux of fatty acids & triglycerides
- Calcification as chalky white deposits (**saponification**) in adipocytes – calcium "soaps"
  - **PANCREATITIS**: leakage of pancreatic enzymes (**lipase**) releases FA & causes necrosis of peripancreatic fat via saponification (*Pathoma: pancreatitis exhibits 2 forms of necrosis*)
  - **TRAUMA**: **crush injury** to the **breast**

4. Caseous necrosis: *necrosis in which the tissue becomes a soft, dry, crumbly mass resembling **cheese**, usually caused by **mycobacterial** infection or fungal infections*



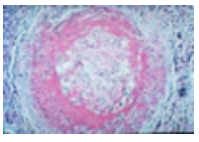


- **TUBERCULOSIS!!!!** = "CHEESE LIKE"
- Type of STRUCTURELESS coagulative necrosis
- Surrounded by **macrophages & giant cells** (granulomatous inflammation) & fibrosis

5. Gangrenous necrosis: *cell death caused by a combination of ischemia & superimposed bacterial infection, combining the features of coagulation & liquefactive necrosis*

- DRY GANGRENE: type of coagulative necrosis where there is ischemia that leads to gradual mummification
  - NOT ASSOCIATED WITH INFECTION
  - **CLASSIC EXAMPLE** – DIABETIC FOOT – *occlusive peripheral atherosclerotic vascular disease*
- WET GANGRENE: type of liquefactive necrosis due to a bacterial superinfection
  - Putrefaction (tissue rotting) due to ischemia of infected tissue & inability to clear necrotic tissue

6. Fibrinoid necrosis: *deposition of fibrin & other proteins in the walls of blood vessels (afferent renal arterioles in malignant hypertension), often accompanied by an inflammatory infiltrate within the walls & thrombosis of the vessel lumen; also called necrotizing arteriolitis*



- Most commonly due to immune complex deposition in blood vessel walls (**VASCULITIS**) or due to **malignant HTN**
- Necrosis causes leakage & deposition of fibrin & other plasma proteins
- Bright pink staining of the wall seen in biopsy

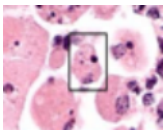
MORPHOLOGIC SPECTRUM OF IRREVERSIBLE INJURY

Note: the 'reversible cell injury characteristics' can also be seen, but once loss of the nucleus begins, it is then irreversible.

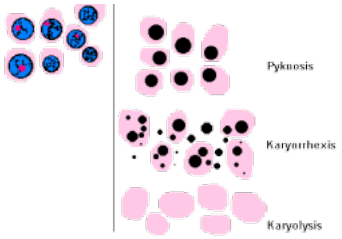
- Increased intracellular volume (cell swelling), cytoplasmic eosinophilia
- Plasma membrane blebbing
- Chromatin clumping & redistribution
- Nuclear shrinkage & condensation – **PYKNOSIS**[HY1]
- Nuclear fragmentation (**KARYORRHEXIS**[HY1]) and/or dissolution (**KARYOLYSIS**[HY1])
- Cell ghosts (or **amorphous debris**)

***PYKNOSIS:** a thickening, especially degeneration of a cell, in which the **nucleus shrinks in size** & the chromatin **condenses** to a solid, structureless, **basophilic** mass or masses

***KARYORRHEXIS:** **fragmentation** of a pykontic cell nucleus in which the chromatin disintegrates into formless granules



***KARYOLYSIS:** the swelling of the nucleus of a necrotic cell & fading of the chromatin as it becomes less basophilic owing to deoxyribonuclease activity; **dissolution of the cell nucleus**



HOW TO KILL A CELL

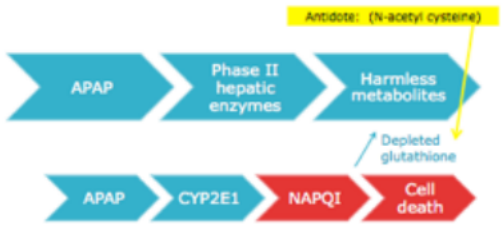
- *Deprive O_2, deprive it of nutrients, infection*[HY1]*, poison, radiation, reperfuse it, bystander effect, self-destruction*

VIRAL INFECTION

- DIRECT CYTOPATHIC EFFECT: virus infecting the cell directly leads to lethal injury
- INDIRECT KILLING: virus infects cell, viral genome incorporated into host cell, viral proteins synthesized, host immune system detects viral proteins & kills cell

CHEMICAL-INDUCED

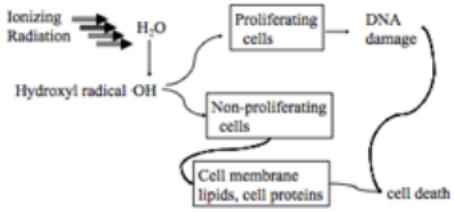
- DIRECT TOXICITY: direct interference with critical molecular components
  - **Mercuric chloride** – binds to sulfhydryl groups of cell membrane proteins
  - **Cyanide** – knocks out cytochrome oxidase (key OxPhos enzyme)
  - **ChemoRx agents** (**taxols**: microtubular derangements within mitotic apparatus)
- INDIRECT TOXICITY VIA METABOLITES: indirect toxicity following conversion from biologically inactive forms to active metabolites
  - Carbon tetrachloride (CCl_4) → $\cdot CCl_3$ HY1 – *dry cleaners → lipid peroxidation*
  - **ACETAMINOPHIN TOXICITY ***
    - At toxic dosages, the liver's normal glutathione reserves are depleted so the excess APAP is metabolized by the CYP2E1-P450 system, which produces NAPQI. NAPQI will covalently bind vital proteins & nucleic acids in hepatocytes, which will elicit release of cytokines from liver macrophages (Kupffer cells) causing hepatocellular death.
    - At normal doses, NAPQI is converted to harmless metabolites via glutathione
    - In an alcoholic, this process is exacerbated!

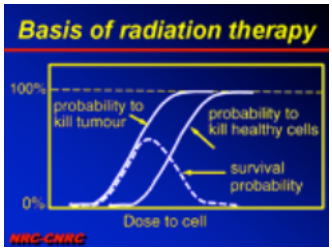


- INDIRECT TOXICITY VIA IDIOSYNCRATIC RXN (hypersensitivity/immune): drug injury might not be directly by drug itself (nor by a metabolite), but instead, might be a triggered host inflammatory reaction
  - Mechanism is unknown; drug toxicity causing acute renal failure via acute interstitial nephritis

RADIATION

- Ionizing radiation is meant to kill proliferating cells





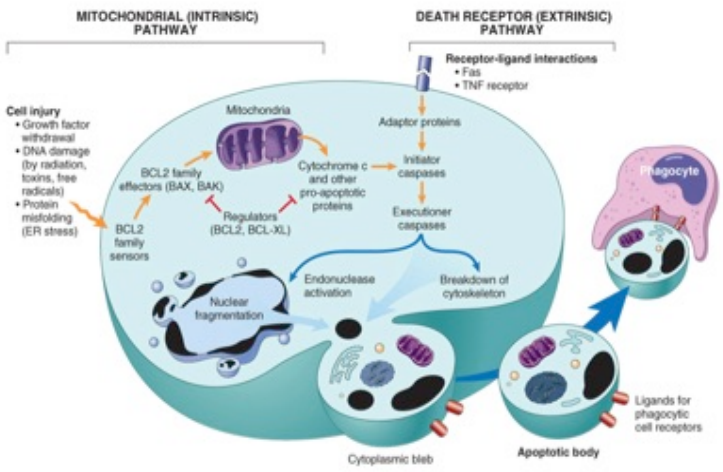
REPERFUSION INJURY

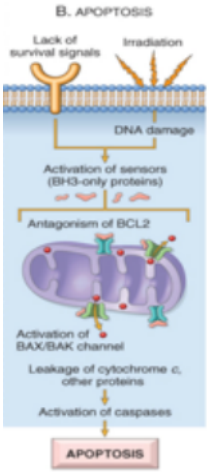
- *Resumption of blood supply & oxygenation to ischemic tissue may lead to further injury & tissue destruction*
- Proposed mechanisms: **ROS**, Ca^{2+}, **inflammatory** cell influx, complement system
- Ischemia causes inflammation because of the development of necrotic tissue. Inflammatory cells naturally produce ROSs to clear the necrosis. Therefore, *reperfusing the area with O_2-rich blood will cause the ROSs to react with the reintroduced O_2 – This increases the ROS amount, causing increased tissue damage*
  - **Iron** (Fe^{2+}) plays a major role in this due to the **Fenton Reaction** generating **hydroxyl radicals**
- *i.e. leads to continued rise in cardiac enzymes (**troponin**) after reperfusion of infarcted myocardial tissue*

APOPTOSIS: *aka "suicide"; a morphologic pattern of cell death affecting **single cells**, marked by **shrinkage** of the cell, **condensation** of chromatin, formation of cytoplasmic blebs, & **fragmentation** of the cell into membrane-bound apoptotic bodies that are eliminated by phagocytosis (via macrophages)*

APOPTOSIS FROM ROBBINS

- *Results from activation of enzymes called caspases*
- ***INTRINSIC PATHWAY** results from increased permeability of the mitochondrial outer membrane with consequent release of death-inducing (pro-apoptotic) molecules from the mitochondrial intermembrane space into the cytoplasm. The release of mitochondrial pro-apoptotic proteins initiates the suicide program of apoptosis & is tightly controlled by the **BCL2** family of proteins.*
  - ***ANTI-APOPTOTIC: BCL-2, BCL-XL, MCL1** – These proteins keep the mitochondrial outer membrane impermeable by preventing the leakage of cytochrome c & other death-inducing proteins into the cytosol.*
  - ***PRO-APOPTOTIC: BAX & BAK** – Upon activation, BAX & BAK oligomerizes within the outer mitochondrial protein & promote mitochondrial permeability by forming a channel in the outer membrane that allows leakage of cytochrome c from the intermembranous space.*



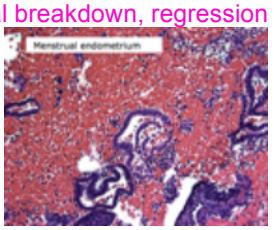


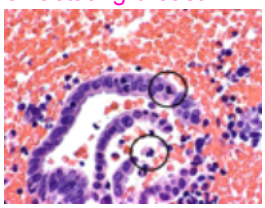
APOPTOTIC PATHWAYS

- *According to Pathoma, apoptosis is mediated by caspases that activate proteases & endonucleases. (Proteases break down the cytoskeleton. Endonucleases break down DNA.) Caspases are activated by 3 different pathways.*
- INTRINSIC/MITOCHONDRIAL PATHWAY
  - Cell injury, DNA damage, & decreased hormonal stimulation → inactivation of **Bcl2**
  - Lack of Bcl2 → BAK/BAX pore formation → **cytC** leakage from mitochondria & **activation of caspases**
- EXTRINSIC/DEATH RECEPTOR PATHWAY
  - FasL-Fas death receptors *(i.e. negative selection of T cell in the thymus)*
  - *TNF-TNFR*
- *CYTOTOXIC $CD8^+$ T CELL-MEDIATED PATHWAY: perforins & granzymes*

PHYSIOLOGIC APOPTOSIS

- **Embryogenesis**: urachus, umbilicus, ductus arteriosis, thymus
- **Hormonal**: cyclic endometrial breakdown, regression of lactating breast





Apoptotic endometrial epithelial cells

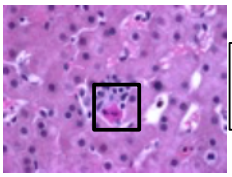
- "**Surplus**": immature lymphocytes, epithelial cells in intestinal crypts, inflammatory cells following resolution of inflammation

PATHOLOGIC APOPTOSIS

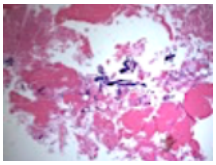
- Radiation, drugs (ChemoRx), hypoxia, misfolded proteins, infection, atrophy (hormonal withdrawal & obstruction)

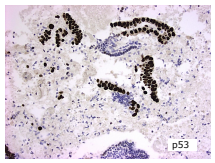
APOPTOSIS CAUSED BY INFECTION

- Chronic viral infections (i.e. hepatitis C) can be latent for many years (decades)
- Viral activation = "active" **hepatitis** – can lead to liver dysfunction, tissue damage, & cirrhosis
- Doctors are able to assess the current status of the patient's disease via tissue biopsies:



LIVER BIOPSY – *Single apoptotic cell is seen – **not necrosis**.*
Extracellular, round, eosinophilic Councilman bodies-HY1





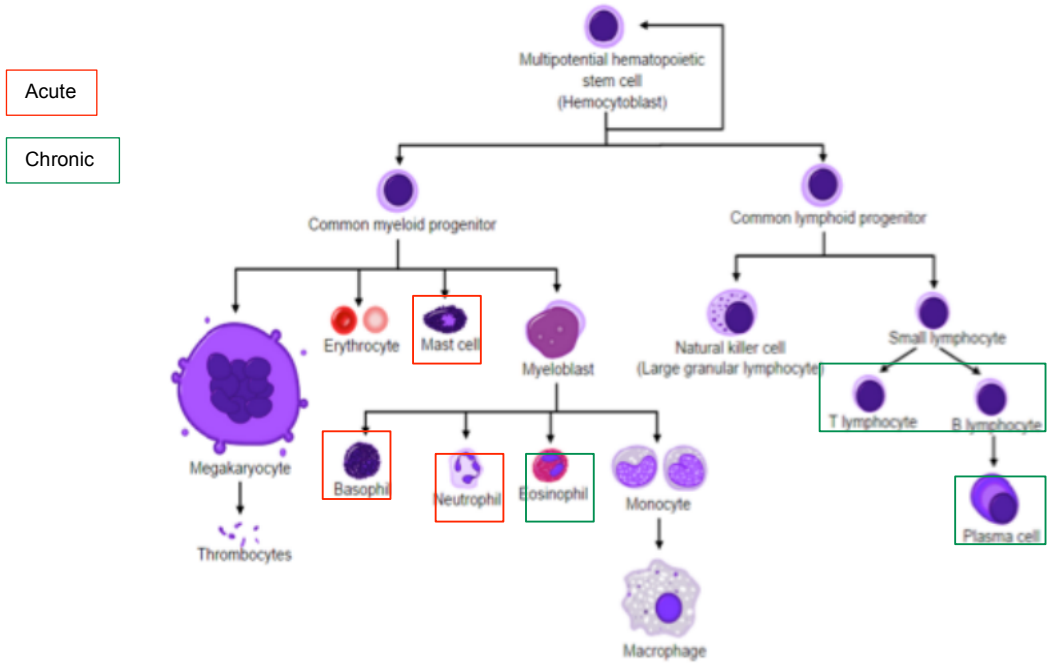
ENDOMETRIAL BIOPSY – *Malignancy seen – histological staining for p53 then performed (right). Cells have proliferated in unregulated manner – not enough apoptosis.*

*******HY[1]	NECROSIS	APOPTOSIS
Stimuli	Hypoxia, toxins **ALWAYS PATHOLOGIC**	Physiologic & pathologic
Histology	**Many** confluent cells Cellular swelling Coagulation necrosis, eosinophilia Disruption of organelles	**Single** cells Cell shrinkage Chromatin condensation Apoptotic bodies
DNA Breakdown	[EXTRINSIC MECHANISM] Random, diffuse ATP depletion **Cell membrane injury & leakage** Free radical damage	[INTRINSIC MECHANISM] Internucleosomal gene activation Endonuclease **Cell membrane intact**
Tissue Reaction	Brisk **inflammatory** response	**No inflammation** Phagocytosis of apoptotic bodies *(via macrophages)*
Resolution	Takes time	Rapid

INFLAMMATION

- **Rubor**: redness & **Calor**: warmth
  - *Due to vasodilation (increased blood flow) & occurs via relaxation of arteriolar smooth muscle*
  - ***Key mediators**: histamine, prostaglandins, & bradykinin*
- **Dolor**: pain
  - ***Key mediators**: bradykinin & PGE – sensitize sensory nerve endings*
- **Tumor**: swelling
  - *Due to leakage of fluid from postcapillary venules into the interstitial space (exudate)*
  - ***Key mediators**: histamine (endothelial cell contraction) & tissue damage (endothelial cell disruption)*

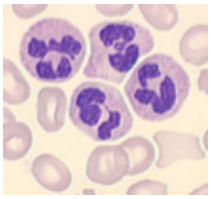
**Refer to this image throughout the remainder of this section*

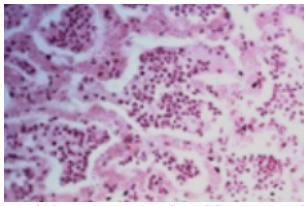


CELLS OF ACUTE INFLAMMATORY RESPONSE

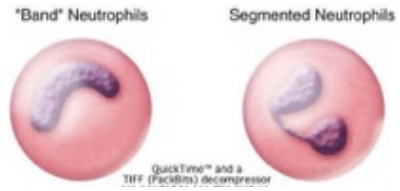
POLYMORPHONUCLEAR LEUKOCYTES – NEUTROPHILS

- Aka PMN, polys, segmented leukocytes, neutrophils
- Finely granular cytoplasm with multi-lobed nucleus
- Have membrane receptors, phagocytic function, lysosomes loaded with free radicals & enzymes for internal & external use



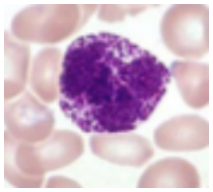


**Acute lobar pneumonia with neutrophils*



BASOPHILS & MAST CELLS

- Very dense cytoplasmic granules with proteins & vasoactive substances – *histamine, leukotriene, proteases*
- Pre-packaged for *rapid, immediate* response
- High density of IgE receptors

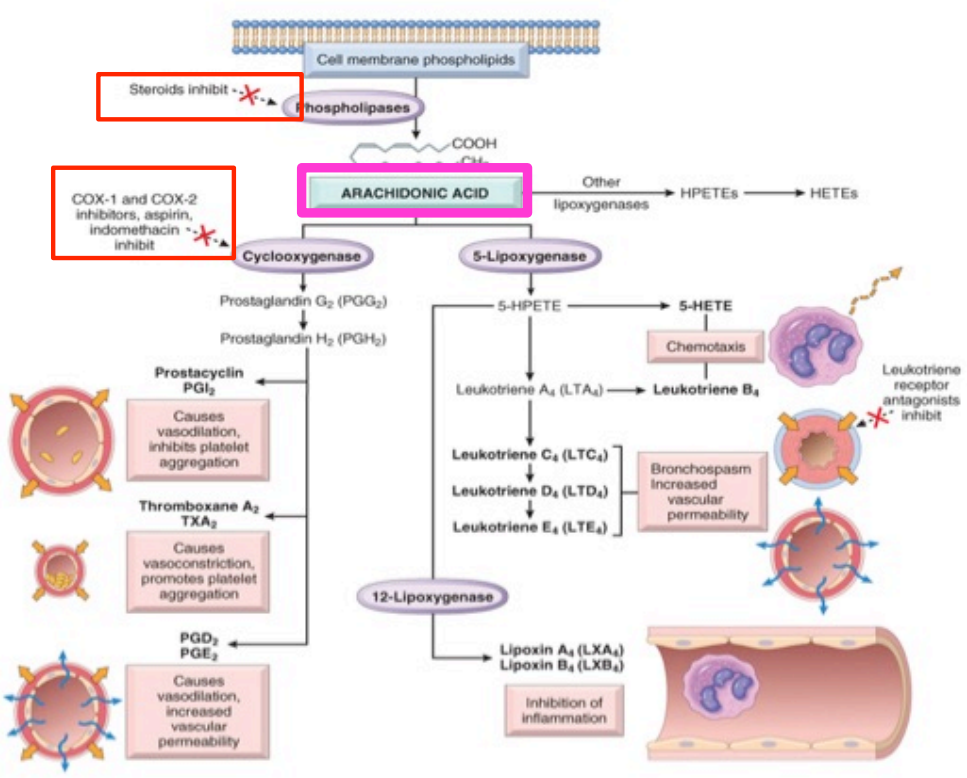


PLATELETS

- Hemostasis – clot formation – & inflammatory mediators
  - *Histamine & TXA*

SUBSTANCE	SOURCE	ACTION
Histamine	Mast cells, basophils, platelets	Vasodilation, increase vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever (PGE)
Leukotrienes	Mast cells, leukocytes	Increase vascular permeability, chemotaxis, leukocyte adhesion & activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Endothelial activation; systemic effects, including fever, hypotension (shock), metabolic abnormalities
Chemokines (IL-8)	Leukocytes, mast cells	Vasodilation, increase vascular permeability, leukocyte adhesion/chemotaxis/degranulation/ oxidative burst
Complement components	Plasma *(synthesized in liver & are circulating)*	Leukocyte chemotaxis, direct target killing (MAC), mast cell stimulation
Kinins	Plasma *(synthesized in liver & are circulating)*	Increase vascular permeability, smooth muscle contract, vasodilation, pain

VASODILATION	VASCULAR PERMEABILITY	CHEMOTAXIS, LEUKOCYTE RECRUITMENT & ACTIVATION	FEVER	PAIN	TISSUE DAMAGE
Histamine Prostaglandin	Histamine Serotonin C3a & C5a LTC_4, LTD_4, LTE_4	TNF, IL-1 Chemokines (IL-8) C3a, C5a LTB_4	IL-1, TNF PGE	PGE Bradykinin	Lysosomal enzymes of leukocytes ROS



**Phospholipases (i.e. PLA_2) release ARACHIDONIC ACID from cell membrane phospholipids. Arachidonic acid is the precursor to prostacylcins, prostaglandins, & thromboxanes (via cyclooxygenase pathway) and also to leukotrienes (via lipoxygenase pathway).*

- *Phospholipases are inhibited by steroids (i.e. cortisol)*
- *Cyclooxygenase pathway enzymes are inhibited by COX1 & 2 inhibitors and NSAIDS (i.e. aspirin)*

****TERMINOLOGY**

- **Stasis**: slowed blood flow
- **Congestion**: increased amount of blood in vessels, usually at a higher concentration & with stasis
  - i.e. CHF, nasal congestion
- **Edema**: accumulation of fluid in the interstitium (intercellular space of tissue)
- **Effusion**: accumulation of fluid in a cavity/space
- **Serous**: watery
- **Sanguineous**: bloody fluid
- **Serosanguineous**: "hallway between"
- ***Fibrinous**: containing activated clotting factors; may be thick & stringy
- **Purulent:** white/green & thick, highly cellular (**THINK**: NEUTROPHILS)
- **Malignant:** associated with cancer (i.e. effusion associated with a large lung mass)

4 STEPS TO GET INFLAMMATORY CELLS TO ACTION:

1. Increase blood flow/volume of blood & SLOW rate of blood flow (*stasis*)
   - Sensing damage, cells in the area release vasoactive mediators (histamine, prostaglandins)
   - **VASODILATION**
2. Increase permeability of blood vessels
   - Cell-derived (*histamine, prostaglandin, LTs*) & plasma-derived (*C3a, C5a, kinins*) vasoactive mediators allow for "gaps" in the vessel membranes
   - Fluid is then able to migrate into interstitium → **EDEMA**
     - Focal edema: in a specific area
     - Diffuse edema: throughout entire body
   - Leukocytes also migrate into interstitium
3. Actively recruit & attract inflammatory cells
   - *As blood flow slows, marginization & rolling of leukocytes occurs with help of selectins. Damaged cells/matrix or stimulated inflammatory cells secrete cytokines – ****IL-1, TNF** – inducing increased expression & affinity of binding proteins on leukocytes & endothelial cells. "Loose" contact now becomes tight adherence via **integrin & ICAM-1.***
   - ***ROLLING**: E-Selectins on ECs; Sialyl Lewis on leukocytes
   - ***TIGHT BINDING/ADHESION**: ICAM-1 on ECs; LFA-1 on leukocytes
   - ***TRANSMIGRATION**: PECAM, Actin
4. Once they arrive, direct leukocytes to the action
   - *Chemokines (IL-8)
   - *C5a (C3a not as important)
   - *AA metabolites (LT-B4)

TRANSUDATE	EXUDATE
Usually clear, thin, watery – dilute	Usually cloudy +/- thick
Low protein content	High protein content
Low LDH, cholesterol	High LDH, cholesterol
Low cellular content	High cellular content
Pressure problem* (hydrostatic oncotic)	**Inflammatory problem***
CHF, nephrotic syndrome*	Infection, autoimmune disease*

**usually*

EFFUSION EXAMPLE

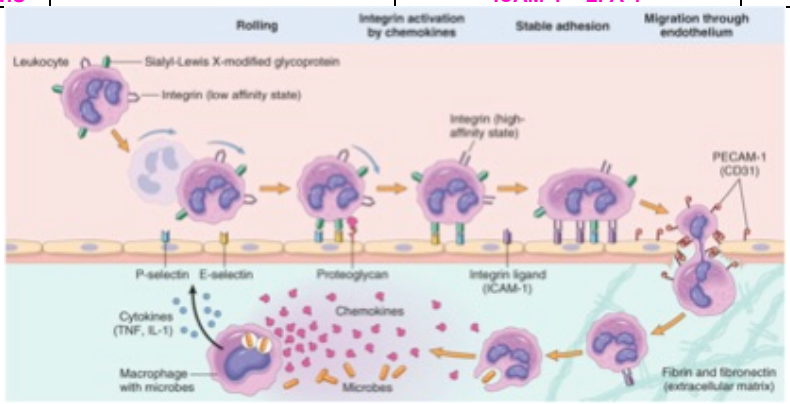
77 y/o patient with CHF presents with SOB. PE: diminished breath sounds on R side, 3+ pitting edema bilaterally. CXR shows pleural effusion on R. Thoracentesis performed – slightly cloudy fluid

- Is this an exacerbation of patient's CHF? Or is this an inflammatory problem?
  - Lab shows high protein content & cloudy fluid → **EXUDATE**
  - Inflammatory problem → PNEUMONIA (para-pneumonic effusion)

****FIBRINOUS EXUDATE IN PERICARDIUM (PERICARDITIS)**

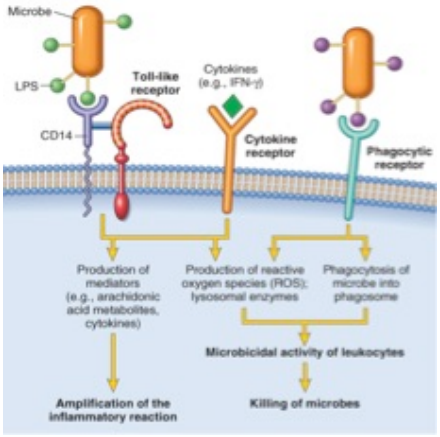
- Inflammatory exudate surrounding the heart
- Highly granular
- PE finding: you can hear the rub of the pericardium/rough surface

MARGINATION & ROLLING	ACTIVATION	ADHESION	MIGRATION
SELECTIN family of binding proteins on endothelium (stimulated by cytokines TNF, IL-1) **E-SELECTION + SIALYL LEWIS**	INTEGRIN on leukocyte is inactive, until chemokines activate it	Firm adhesion via activated **INTEGRIN** on leukocytes & **tight** binding with its ligand **ICAM-1** **ICAM-1 + LFA-1**	CD31 (PECAM-1) helps draw leukocyte into interstitial space **PECAM-1 + ACTIN**



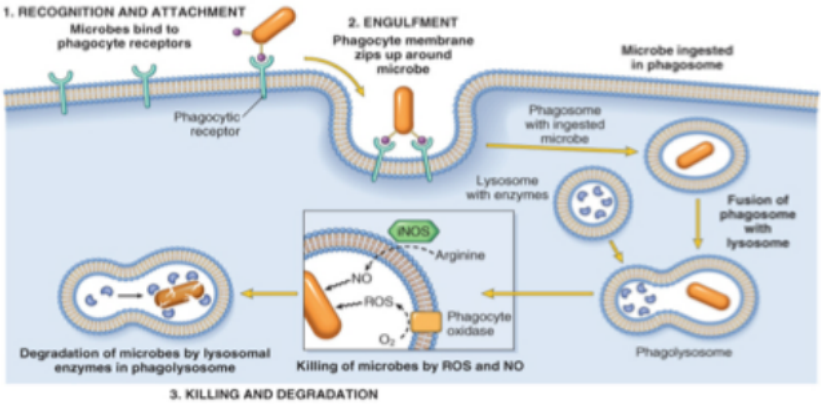
ACTIVATION

- Toll-like receptor (**TLR**) associated with **CD14** recognizes PAMPs (i.e. LPS) on microbes & leads to increased protein synthesis to produce metabolites derived from arachidonic acid & cytokines to *further amplify the inflammatory response*
- Lysosomal enzymes produced to digest what has been ingested by the leukocyte

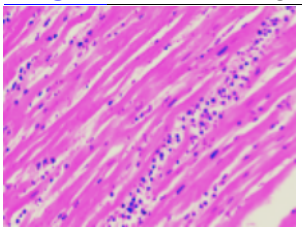


PHAGOCYTOSIS

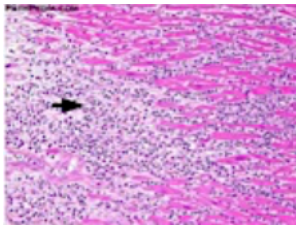
- Phagocytosis involves microbe binding to receptors on leukocyte membrane, engulfment, & fusion of the phagocytic vacuoles with lysosomes. This is followed by destruction of ingested particles within the phagolysosome by lysosomal enzymes & by ROS & NO.



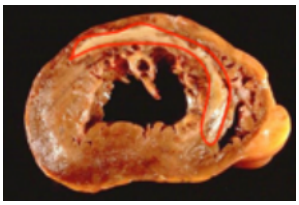
ACUTE INFLAMMATION – MYOCARDIAL INFARCTION



24 hours post-MI: Coagulative necrosis is ongoing with pyknosis of nuclei. Contraction band necrosis (losing striations). Basophilic cells seen are neutrophils beginning to infiltrate the myocardium. (No gross change.)



Day 2-3: Coagulative necrosis with loss of nuclei & striations. Arrow shows heavy neutrophilic infiltrate. The necrotic myocytes are being replaced by collection of neutrophils to initiate the process of acute inflammation & repair.



Visible lesion – mottling with yellow-tan discoloring in center of affected area, surrounded by a border of necrosis & inflammation.

OUTCOMES OF ACUTE INFLAMMATION

- Complete resolution & healing – *macrophages come in 2-3 days after inflammation begins & secrete anti-inflammatory cytokines IL-10 & TGF*
- Healing by **connective tissue** replacement (scar/fibrosis)
- ***Persistent inflammation**
  - Acute response not completely successful
  - Possibly with isolation of offender (abscess – *acute inflammation surrounded with fibrosis*, granuloma)
  - Or, progression to ***chronic inflammation*** – *macrophages activate $CD4^+$ T helper cells to secrete cytokines promoting chronic inflammation*
  - +/- interference with normal healing process

	ACUTE INFLAMMATION	CHRONIC INFLAMMATION
ONSET	Rapid onset, *non-specific* *Response to infection or tissue necrosis*	Slow onset, *specific* *Response to persistent infection; viral, Mycobacterial, parasitic, or fungal infection; autoimmune; foreign material; some cancer*
CELLULAR INFILTRATE	**Neutrophils***, mast cells, basophils	**Lymphocytes**, **macrophages**, **plasma cells**, eosinophils
TISSUE INJURY	Local, often mild & limited	Variable; can be severe
FIBROSIS	Variable	Variable; can be severe
CLINICAL PRESENTATION	Prominent signs/symptoms	Variable; signs/symptoms can be subtle

**Acute & chronic patterns are seen in many different tissues*

	ACUTE	CHRONIC
GASTROINTESTINAL	Appendicitis	Crohn's colitis
HEART	Myocardial infarction	Transplant rejection
KIDNEY	Acute tubular necrosis	Diabetic nephropathy
CNS	Meningitis	Multiple sclerosis
LUNG	Asthma	Asthma

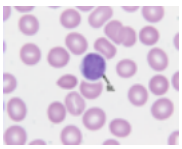
CHRONIC INFLAMMATION

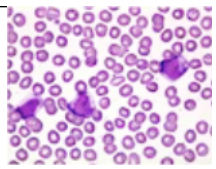
- *Inflammatory response of prolonged duration (weeks or months) in which inflammation, cell injury & death, and attempts at healing are all occurring simultaneously*
- Sources of persistent inflammatory stimuli:
  - Persistent infection (syphilis, HIV, Lyme disease)
  - Prolonged exposure or accumulation (acid, ruptured cutaneous cyst, atherosclerosis)
  - Autoimmune disease (Hashimoto thyroiditis, pemphigus vulgaris)
  - Environmental allergies or toxicity
- A chronic inflammatory process may arise by evolution of initial acute inflammation, BUT NOT ALWAYS. Some disease processes manifest as slow insidious onset of smoldering chronic inflammation, without any preceding 'acute' inflammatory event.

CELLS OF CHRONIC INFLAMMATORY RESPONSE

LYMPHOCYTES

- Immune response: Humoral (B) or cell-mediated (T)
- Mostly antibody driven, either circulating or membrane-bound
- Minimal lysosomes
- "Memory" & specificity
- Variant: NK cells: potent, innate cidal activity when non-self antigens are detected

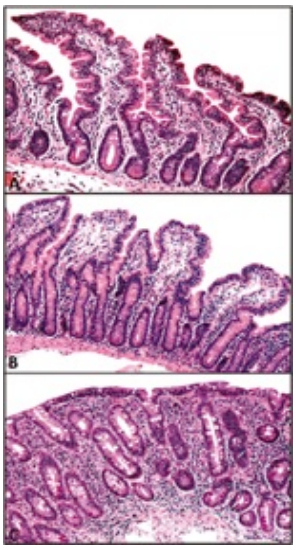




Reactive lymphocyte

CELIAC DISEASE – CELIAC SPRUE

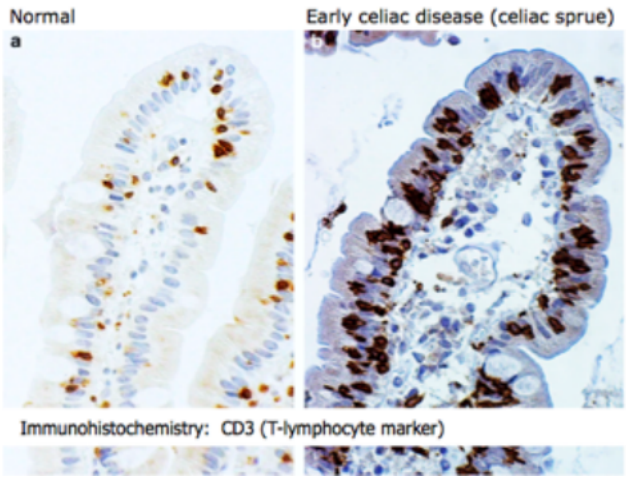
- 6 months history of abdominal pain, diarrhea, bloating
- EGD shows normal esophagus, normal stomach, & flattening & scalloping of duodenum
- **INTRAEPITHELIAL T LYMPHOCYTES**

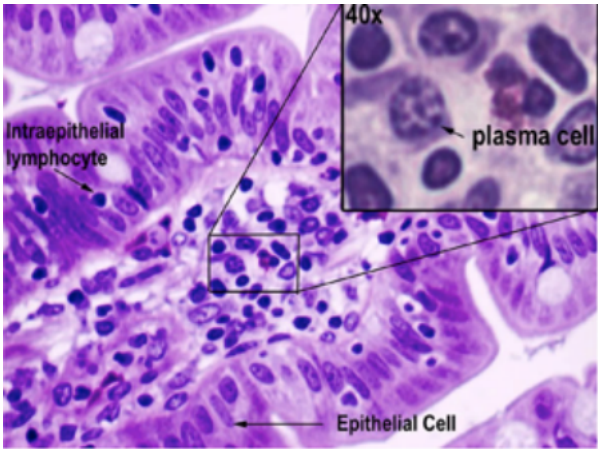


Normal duodenal mucosa

Patient biopsy
Note: Loss of surface area

Patient biopsy after 3 months of non-compliance with Rx

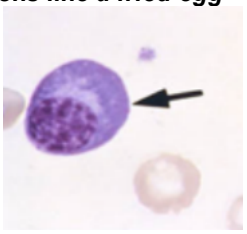


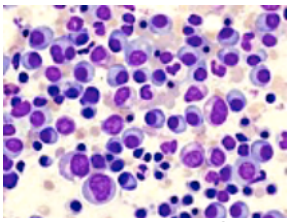


This image is from UCSF med school iROCKET page. It is showing the human jejunum. I have put it in because I thought it was a good demonstration of the difference between the plasma cell & intraepithelial lymphocyte.

PLASMA CELL – "SPECIALIZED LYMPHOCYTE"

- Antibody production
- Morphologic features:
  - Larger than lymphocyte, more abundant cytoplasm, distinct golgi zone clearing, coarse climbed chromatin
  - ***It looks like a fried egg***



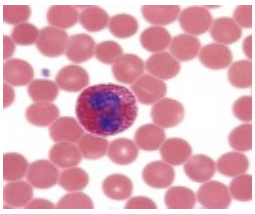


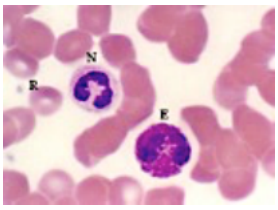
MULTIPLE MYELOMA

Golgi zone clearing seen due to heavy Ab production in plasma cells

EOSINOPHILS

- Bi-lobed nucleus & bright red granules
- Granules contain **major basic protein** (highly cationic protein with potent toxicity)
- Respond to the same chemotactic & activating molecules as neutrophils
- Broad clinical spectrum (but few key pathologic processes)
  - ***Parasite infection**
  - ***Allergy/hypersensitivity**
  - Chemical exposure (acid reflux), air exposure (pneumothorax), other chronic inflammatory responses

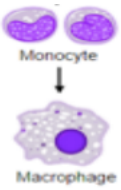




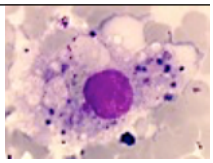
(In comparison to neutrophil)

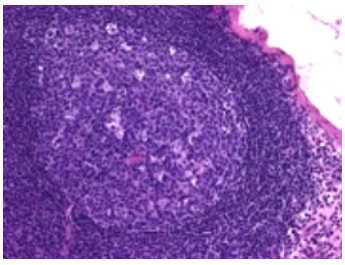
MONOCYTE → MACROPHAGE

- "The Clean-Up Crew" & initiator of adaptive immunity
- Aka **histiocyte**, dendritic cell, Kupffer cell, microglial cell
- Specializes in **phagocytosis** (removal of microbes & debris), cytokine production, & antigen presentation (APC)
- Also functions in **tissue repair** – some of the same mediators that activate & advance the inflammatory response among macrophages can also have opposite effect – *aka suppress inflammation* – in order to promote healing & recovery

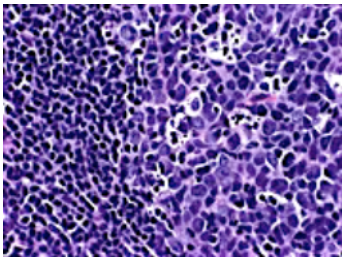


Larger cells, a lot of cytoplasm, larger nucle vesicles in cytoplasm





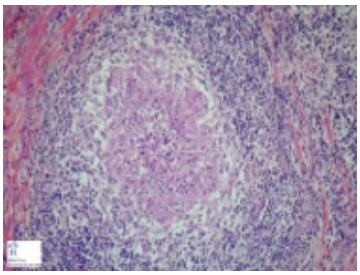
Lymph node – macrophages surrounded by empty spaces; antigen presentation happening; lymphocyte maturation



Lymph node – *higher magnification of image above*

GRANULOMATOUS INFLAMMATION

- A localized or nodular collection of epithelioid **macrophages**, often with one or more of the following features:
  - Multi-nucleated giant cells
  - Peripheral rim of lymphocytes (T cells)
  - Fibrosis
  - Co-existing acute inflammation (central)
  - **Necrosis** (microscopic): *caseating*
    - Usually due to tuberculosis or fungal infections; *non-caseating granulomas are typically not infectious, rather due to foreign material, sarcoidosis, Crohn's, etc.*
- Etiology of granulomas
  - Often a response to ingested material that cannot be further broken down
    - *Mycobacteria* (mycolic acid)– *Tuberculosis! – caseating!*
    - Fungi
    - Foreign body reaction – "suture granuloma"
  - **Sarcoidosis**: non-infectious process that typically results in non-caseating granulomatous inflammation
  - Crohn's disease

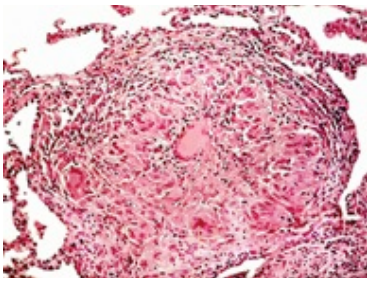


NON-CASEATING GRANULOMA

Epithelioid macrophages: central; pink character because there is a lot of cytoplasm

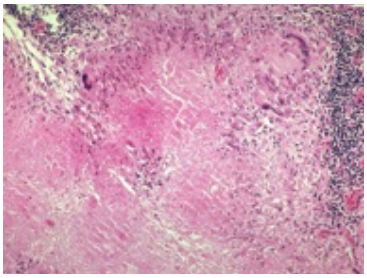
Rim of **lymphocytes** – dark small cells

Surrounded by **collagen** – fibular linear appearances (**fibrosis**)



NON-CASEATING GRANULOMA OF THE LUNG (you can see alveolar spaces) – SARCOIDOSIS

Multinucleated giant cell – not always in granuloma, but typically characteristics of it



(CASEOUS) NECROTIZING GRANULOMA**

You can hardly see anything other than amorphic necrotic pink debris.

Upper right corner: large multinucleated giant cell → fungal or Tb

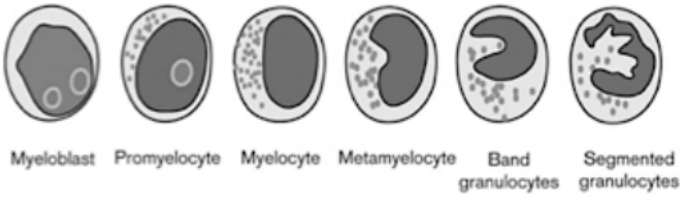
CHRONIC INFLAMMATION

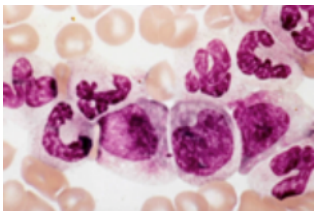
- Mediators:
  - **T-lymphocytes → IFN-γ**
    - **IFN-γ** is detected by macrophages, which then trigger pro-phagocytic actions & release microbicidal products (ROS, lysosomal enzymes) & cytokines (TNF, IL-1, chemokines)
  - T lymphocytes, ECs, etc. → IL-4, IL-13
    - Stimulate a subpopulation of macrophages without any microbicidal capacity
  - **Eosinophils →** major basic protein
    - Microbicidal & anti-parasitic function
    - Potent & toxic (not only to parasites, but also causes epithelial cell lysis) → tissue damage when eosinophils are prevalent (allergy response)
  - Bacteria → endotoxin

SYSTEMIC EFFECTS OF INFLAMMATION

- Most cytokines have rapid action, short half-life
- **TNF** & **IL-1** → **hypothalamus*** → **fever** (thermoregulation)
  - Other effects: Increase pulse (tachy), decreased sweating, chills/rigor, somnolence, malaise, anorexia
- "Acute phase reactants"
  - C-reactive protein, fibrinogen, transferrin
  - Lab can assist in determining if inflammation is present
    - ****ESR: ERYTHROCYTE SEDIMENTATION RATE**
      - Capitalizes on the fact that fibrinogen is elevated during inflammation
      - Presence of increased fibrinogen causes erythrocytes to cling together & settle in blood more rapidly than if fibrinogen was low/normal
      - Analyzer optically measures rate of RBC sedimentation in a pipette of blood
    - ****CRP: C-REACTIVE PROTEIN**
      - Synthesized in the liver; stimulated by cytokines
      - Bind to damaged cells (& microbes) & assists with opsonization & complement fixation
      - *Generally, CRP is a more specific marker of inflammation than ESR*
    - Complete Blood Count (CBC) with differential
      - **Leukocytosis** – elevated number of circulating WBCs
        - Elevated neutrophils = bacterial infection
        - Elevated lymphocytes = viral infection

        ***But not always**
      - **Leukopenia** – paradoxical decrease in numbers of circulating WBCs (typhoid, Tb, etc.)
    - ****Clinical Concept – "THE LEFT SHIFT"**
      - This means that a particular population of cells is "shifted" towards more immature precursors
      - i.e. neutrophils – in normal blood, neutrophils are virtually all mature (segmented); in a left shift, you see mature neutrophils but mostly immature neutrophils
      - Systemic effects – if the body needs them 'now' before they are actually matured; **significant because it points to a bacterial infection**





REPAIR AND HEALING

GENERAL REQUIREMENTS FOR HEALING PROCESS TO *COMPLETELY* RESOLVE*:*

- Mild injury
- Mediator neutralization
- Return to vascular homeostasis – normalization of vascular permeability
- Effective removal of dead cells & material
- Readily available supply of replacement cells with regenerative ability

REGENERATION

- Skin, GI, tract epithelium, hematopoietic cells of bone marrow
  - Requirements: stem cells/progenitor cells to repopulate & GFs to tell them
- Solid organs with stable populations:
  - Very limited capacity: pancreas, adrenal, thyroid, lung
  - ****Compensatory response: KIDNEY**
  - ***Notable exception for solid organ regenerative capacity**: LIVER (normal hepatocyte regeneration)
    - Quiescent cells promoted to enter cell cycle to regenerate tissue
    - *After a partial resection, regeneration of the liver occurs via compensatory hyperplasia. Each hepatocyte produces additional cells & then reenters quiescence*

DEVITALIZED (DEAD) TISSUE:

- Pro-inflammatory mediators gone, neutrophils exit, clean-up of cell debris by **macrophages** → repair

**SCAR FORMATION

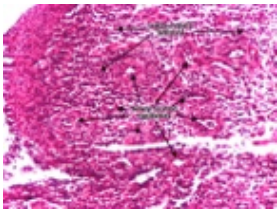
- **SCAR**: common mechanism to *repair* damaged tissue that cannot completely resolve or regenerate

1. **Angiogenesis:** *get supplies*
2. **Granulation tissue formation:** *start rebuilding*
3. **Fibroblast proliferation:** *rebuild fully*
4. **Connective tissue/scar tissue formation:** *rebuilders leave/die*

1. ANGIOGENESIS

- Early role of **VEGF (vascular endothelial growth factors) & **FGF (fibroblast growth factors); **PDGF**, **NO**, & angiopoietins
  - Initial recruitment of leading 'tip' endothelial cell to bud out from existing capillary
  - Basement membrane degradation with pericyte detachment
  - Endothelial & pericyte growth to elongate vascular stalk
  - **Bevacizumab (AVASTIN)** – targeted chemotherapy – Anti-VEGF Ig
- ****MMPs – matrix metalloproteinases**
  - Degrade existing basement membrane
  - Degrade ECM proteins to allow for **remodeling** & construction of new scaffolding to support new vessel
- ***NOTCH signaling pathway***: planner/coordinator to ensure proper spacing of new vessels

2. **GRANULATION TISSUE



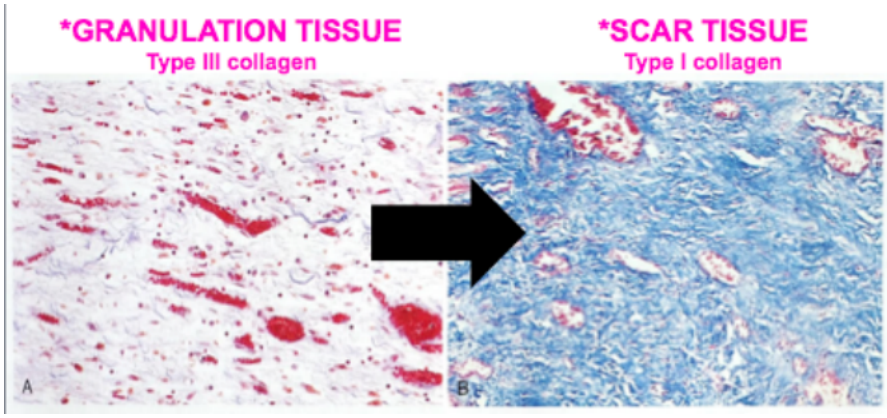
- **IMPORTANT FIRST STAGE OF TISSUE HEALING**
- Very small, newly formed capillaries
- *Loose* ECM, fluid rich, fertile field for growth of vessels & cells
- Cellular components: a few fibroblasts, scattered macrophages**
- ***Collagen type III***
- It is delicate/weak

3. FIBROBLAST MIGRATION & PROLIFERATION

- Rebuilding
- Cytokines & GFs produced by **macrophages** guide them, especially PDGF, FGF, **TGF-β****
  - Fibroblasts synthesize & deposit collagen type III
  - Help to limit & terminate inflammatory response

4. REMODELING/PROGRESSION OF SCAR FORMATION

- **Fewer fibroblasts, more connective tissue** (collagen) → remodeling
- MMPs (matrix metalloproteinases) assist in breaking down existing thin fibrillary collagen (III)
- Structurally stronger, mature ***collagen type I*** in its place (takes time... 3 months-ISH)



TIME LINE OF ISCHEMIC EVENT (MYOCARDIAL INFARCTION)

4-7 DAYS AFTER

- Shift in inflammatory cells – need for cells with a greater capacity to clean up & begin resolution phase
  - **NEUTROPHILS** DISAPPEAR – APOPTOSIS
  - ARRIVAL OF **MACROPHAGES**

1-2 WEEKS AFTER

- Macrophages active in phagocytosis: CLEAN UP
- Angiogenesis becoming well developed at borders of affected zone
- Gross appearance: maximal yellow-tan color, with dark red, depressed borders
- GRANULATION TISSUE

2-8 WEEKS AFTER

- Collagen deposition (type I) with greater maturation & progressively increasing density of fibrous tissue (replacing the thin type III collagen)
- Cellularity decreases
- Gray-white scar grossly recognizable

2 MONTHS AFTER

- MATURE SCAR TISSUE

SCAR vs FIBROSIS

- **SCAR**: organized collagen deposition to **repair & replace** dead tissue
- **FIBROSIS**: increased collagen deposition, usually in broad area & somewhat less organized, often in response to chronic inflammation (sclerosis); *usually not repair from an injury*

****WOUND HEALING**

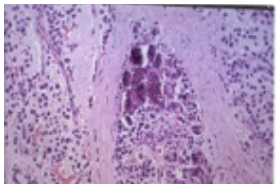
- PRIMARY INTENTION: layers lined up & brought together immediately; *i.e. suturing of surgical incision*
- SECONDARY INTENTION: larger defect, larger volume of granulation tissue, involves wound contraction

****KELOID**

- Scar tissue grows beyond the boundaries of the original wound
- Abnormally excessive *type III collagen* deposition in what otherwise would have been a scar
- African Americans, earlobes

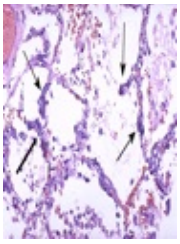
**** DYSTROPHIC CALCIFICATION – DAMAGED AREAS**

- Deposition of calcium in diseased, injured, necrotic, or aged tissue occurring at **NORMAL SERUM Ca^{2+} LEVELS**
- Commonly occurs on cardiac valves or atherosclerotic plaques, neoplasms, granulomas
- Calcification will be deeply basophilic (blue/purple) on a stain
- LOCAL PHENOMENON



**METASTATIC CALCIFICATION

- Deposition of calcium in normal, viable tissues that occurs in the setting of **HYPERCALCEMIA**
- Commonly occurs due to Vitamin D intoxication, chronic renal failure, & primary **hyperparathyroidism**
- Seen in kidney, cardiac valves, & soft tissue
- SYSTEMIC PHENOMENON



Lung

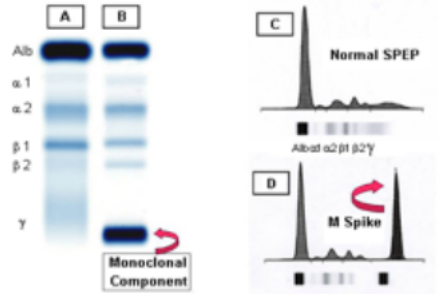
**LYMPHEDEMA

- Scarring of injured lymphatic channels & resulting defect in lymph drainage
  - Post-surgical (lymph node dissection)
  - Post-inflammatory

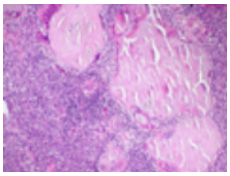
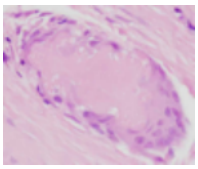
Macrophages: ACTIVITY DURING WOUND HEALING	MEDIATORS
Phagocytosis	ROS, nitric oxide
Debridement	Collagenase, elastase
Cell recruitment & activation	GFs: PDGF, TGF, EGF, IGF Cytokines: TNF, IL-1, IL-6 Fibronectin
Matrix synthesis	GFs: PDGF, TGF, EGF Cytokines: TNF, IL-1, IFN Enzymes: arginase, collagenase Prostaglandins Nitric oxide
Angiogenesis	GFs: FGF, VEGF Cytokines: TNF Nitric oxide

AMYLOIDOSIS

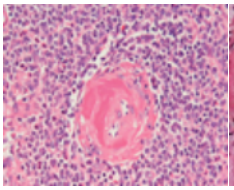
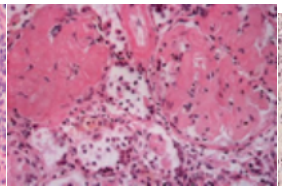
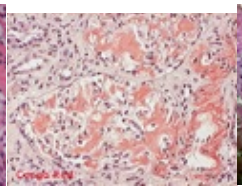
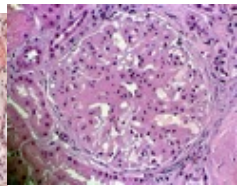
- Material deposition disorder anywhere kidney, heart, liver, nerves, & GI tract
- *Amyloidosis is a misfolded protein that deposits in the extracellular space, thereby damaging tissues*
- Amyloid protein: **THREE TYPES** – *KNOW THESE TYPES!!!!!*
  - ***AL**: **A**myloid **L**ight Chain
    - Composed of light chains (λ more than κ)
    - ***Monoclonal plasma cells or B cell product***
    - Multiple Myeloma, plasmacytoma (solitary tumor), lymphoma, leukemia
    - Monoclonal gammopathy of unknown significants (**MGUS**) – "M spike"



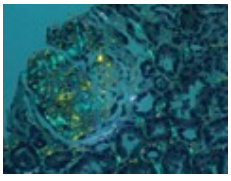
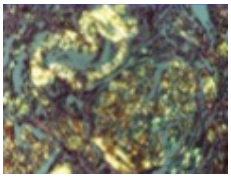
  - ***AA**: **A**myloid **A**ssociated
    - Proteins made by liver called serum amyloid associated proteins (SAA)
    - **Chronic inflammatory states** (chronic infections, autoimmune diseases like **RA**, Hodgkin lymphoma, renal cancer, inherited)
    - **MOST COMMON CAUSE OF AMYLOIDOSIS**
  - ***βA: **B**eta **A**myloid
    - Associated with *Alzheimer disease*
    - Plaques of material in the cortex
- "Beta-pleated sheet"
- ****CONGO RED** positive & apple-green birefringent when viewed microscopically with polarized light
- Systemic (widespread) or localized (in one spot, like a tumor)
- Associated with
  - **Senile Cardiac Amyloidosis** – systemic amyloidosis; characterized by deposition between myocardial fibers; heart is stiff & non-compliant; cannot stretch during diastole
  - May be seen in **Multiple Myeloma**

Pink, amorphous material – before Congo red stain

CONGO RED STAIN turns it even pinker.

Apple-green birefringence of CONGO RED STAIN under polarized light

HEMODYNAMICS

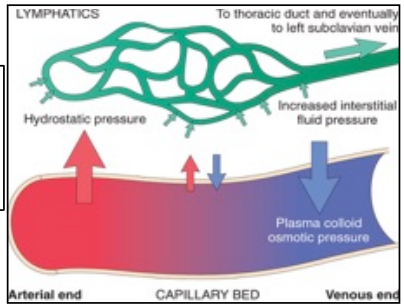
BODY FLUID COMPARTMENTS

- Total body water: ~60% lean body weight
  - Intravascular (blood): 5% of total body water
  - Intracellular: 65% of total body water
  - Extracellular: 30% of total body water
- **INTRACELLULAR COMPARTMENT**: water content is tightly regulated by active metabolic processes controlling inorganic ion (Na^+, K^+) movement across cell membranes; *small perturbations in intracellular water result in severe loss of function*
- **EXTRACELLULAR COMPARTMENT:** most subject to volume change because there are no metabolic systems dedicated to maintaining it in a constant state
  - Major Components: water held in the interstitial matrix (majority), lymph fluid in lymphatics, physiologic fluids (CSF, synovial fluid), small volumes of water in body cavities (pleural, pericardial, peritoneal)

PHYSIOLOGIC FLUID MOVEMENT DURING TRANSIT "CAPILLARY BED"

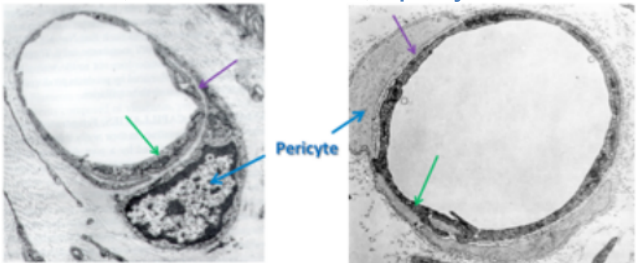
- CAPILLARY BED = CAPILLARY + POST-CAPILLARY VENULE

A small amount of fluid (2-4%) stays in the interstitial space; this fluid is source of lymph & is returned to the vascular system via lymphatics.



Factors influencing fluid transit across capillary walls: CAPILLARY HYDROSTATIC & OSMOTIC forces are normally balanced so that there is no net loss or gain of fluid across the capillary bed. However, INCREASED HYDROSTATIC PRESSURE or DIMINISHED PLASMA OSMOTIC PRESSURE will cause extravascular fluid to accumulate. Tissue lymphatics remove most of the excess volume, eventually returning it to the circulation via thoracic duct. However, if the capacity for the lymphatic drainage is exceeded, tissue EDEMA results.

- **CAPILLARIES**: 7-9 µm lumen diameter
  - Made up of **endothelium**, **basement membrane**, & **pericytes** – *NO SMOOTH MUSCLE!*



- **POST-CAPILLARY VENULE (PCV)**: 10-80 µm lumen diameter
  - Thin walled vascular structures similar to a capillary, except they have a much larger diameter
  - Low pressure with a slow flow rate
  - **TWO IMPORTANT PHYSIOLOGIC FUNCTIONS, IN ADDITION TO BLOOD FLOW TRANSIT:**
    - Site of re-entry of ECF extruded during passage through capillaries
    - Physiologic exocytosis from vascular lumen for cells: lymphocytes, granulocytes, monocytes

TRANSUDATE: thin, low cellular count, protein poor → THINK: INCREASED HYDROSTATIC PRESSURE (i.e. CHF)
EXUDATE: thick, highly cellular, protein rich → THINK: LYMPHATIC OBSTRUCTION, MALIGNANCY, INFECTION

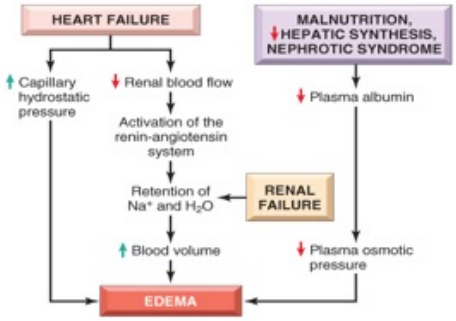
EDEMA: a transudate that leads to an abnormal fluid accumulation in interstitial (extracellular) tissue

- The term is often used with a modifier term:
  - **Interstitial edema**: *increase in interstitial fluid, usually associated with brain or lungs (pulmonary edema)*
  - **Pitting edema**: demonstrated by the examiner making a skin indentation that persists long after removal of the initial pressure
  - **Peripheral edema**

ANASARCA: severe, generalized edema with profound subcutaneous tissue swelling

EFFUSION: transudate fluid that accumulates in a body cavity (pleural, peritoneal); effusions often named by anatomical location:

- **Hydrothorax**: *pleural effusion containing serous fluid*
- **Hydropericardium**: *abnormal accumulation of serous fluid in the pericardial cavity*
- **Hydroperitoneum** (*aka **ascites***): *effusion & accumulation of serous fluid in the abdominal cavity*



PATHOPHYSIOLOGY OF EDEMA (6 MAIN CAUSES)

- *The capacity of tissue lymphatics to drain interstitial tissue must be exceeded. Edema results when interstitial fluid formation overwhelms physiologic lymph drainage; fluid then accumulates in tissue → EDEMA!*
- **INCREASED HYDROSTATIC PRESSURE**
  - **IMPAIRED VENOUS RETURN**: *CHF, constrictive pericarditis, ascites (portal HTN due to liver cirrhosis), venous obstruction (thrombosis, external pressure/mass, LE inactivity with prolonged dependency)*
  - **ARTERIOLAR DILATION**: *heat, neurohumoral dysregulation*
- **REDUCED PLASMA OSMOTIC PRESSURE (HYPOALBUMINEMIA)**
  - *Net movement of fluid into interstitial tissues with subsequent plasma volume contraction: ↓ intravascular volume → ↓ renal perfusion → ↑ production of renin, angiotensin, & aldosterone → salt & H_2O retention*
  - *Nephrotic Syndrome – ↑ protein in the urine → ↓ blood protein; due to many disorders that all damage kidneys; leaky glomerular capillaries; periorbital edema; typically presents with generalized edema*
  - *Liver cirrhosis*
  - *Malnutrition (i.e. Kwashiorkor)*
- **LYMPHATIC OBSTRUCTION → LYMPHEDEMA**
  - *Parasitic (Filariasis – Elephantitis), neoplastic, post-surgical (axillary dissection: breast CA), post-radiation*
- **SODIUM (& WATER) RETENTION**
  - *Causes ↑ hydrostatic pressure (intravascular fluid volume expansion) & ↓vascular colloid osmotic pressure (dilution)* – ↑ total body water & volume due to retention of Na^+ with concurrent H_2O retention
  - Increased volume is **limited to the ECF** because: cells are efficient at maintaining their ICF volume & kidneys are efficient in regulating intravascular volume, *but no mechanism to maintain ECF volume*
  - *Excessive salt intake with renal failure, increased tubular reabsorption of sodium (renal hypoperfusion, increased renin-angiotensin-aldosterone secretion)*
- **INFLAMMATORY EDEMA**
  - Acute inflammation causes increased blood flow, increased movement of cells & fluid into tissue (increased endothelial permeability); type I HSR – *This type of edema is not a true transudate*
- **ANGIOEDEMA**
  - HIVES! – An acute vascular reaction involving dermis, subcutaneous and/or mucosal tissues. Severe edema caused by dilation & markedly increased permeability of capillaries.
  - On skin, giant wheals (hives) develop acutely.
  - *ANGIOEDEMA MAY BE LIFE THREATENING (VASCULAR SHOCK OR LARYNGEAL EDEMA)*

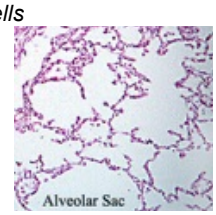
BRAIN/CEREBRAL EDEMA

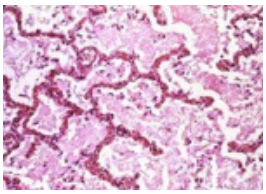
- The CNS has no lymphatics & only limited interstitial space
- **Localized** – adjacent to injury, area hemorrhage, or neoplasm
- **Generalized** – encephalitis, large scale trauma, or obstruction of venous outflow
- In **generalized edema**, the brain is grossly swollen with narrowed sulci & distended swollen gyri & bony table of the skull is unyielding
- **REMEMBER**: the skull interior is non-expansible; any significant swelling of the brain will damage brain tissue if prolonged → BRAIN EDEMA IS ALWAYS A SERIOUS LIFE-THREATENING CONDITION!

ACUTE PULMONARY EDEMA

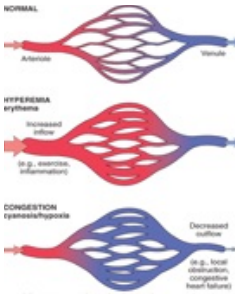
- Accumulation of water & sometimes extravasated plasma in lung alveolar spaces → **pulmonary congestion**
- Frequent cardiac etiology – ***acute left ventricular failure***
  - *Pt presents with dyspnea, orthopnea, S3 gallop. Microscopically, cardiac myocyte hypertrophy with enlarged pleiotropic nuclei and lungs have pulmonary capillary congestion, alveolar edema with intra-alveolar hemosiderin-laden macrophages.*
- May also occur in acute respiratory distress syndrome & pulmonary infections
- With pulmonary edema, **lungs are heavy**; when sectioned the lung reveals frothy, blood-tinged fluid – *edema fluid & extravasated red cells*

NORMAL ALVEOLAR SPACES





PULMONARY EDEMA



HYPEREMIA: ***active process*** resulting from arteriolar dilation

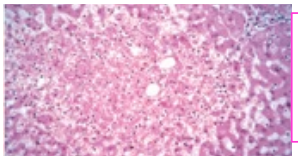
- *Reddened facial skin when embarrassed, flushed appearance with excessive heat*

CONGESTION: ***passive process*** resulting from impaired outflow from a tissue

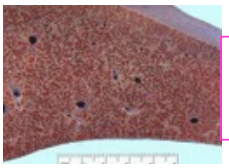
- **Cyanosis:** blue-red color results from accumulation of deoxygenated hemoglobin in blood during conditions of prolonged congestion or stasis

****VASCULAR CONGESTION**

- **ACUTE CONGESTION**: diminished outflow leads to a capillary bed swollen with deoxygenated venous blood, resulting in a blue tinge or tissue appearance even though the increased component is red cells (cyanosis)
- **CHRONIC PASSIVE CONGESTION – *R sided chronic CHF***: causes hemorrhagic necrosis & fibrosis in the **liver**
  - *Pt presents with elevated JVD, dependent edema, ascites, weight gain, pleural & pericardial effusions*
  - A **nutmeg liver appearance** is due to a perfusion abnormality of the liver, usually as result of chronic hepatic venous congestion.



Chronic Passive Congestion & Hemorrhagic Necrosis of Liver: centrilobular necrosis with degenerating hepatocytes & hemorrhage.



Chronic Passive Congestion & Hemorrhagic Necrosis of Liver: Central areas red & slightly depressed when compared with surrounding tan, viable parenchyma forming "**nutmeg liver**"

HEMORRHAGE: extravasation (movement or presence) of blood outside the confines of the intravascular space – *bleeding into extracellular space*; often due to vessel rupture caused by trauma or loss of vascular integrity, i.e. bleeding disorders

1. **HEMATOMA:** accumulation of blood within a tissue; frequently as a localized mass, which distends the tissue & is obviously red
2. **EXTERNAL HEMORRHAGE:** bleeding on body surface or from cavity that communicates directly with exterior (i.e. oral or nasal cavity; can use ***tamponade*** – *increased pressure applied directly to the external site area*)
3. **INTERNAL HEMORRHAGE:** not subject to tamponade – GI tract, ruptured liver **OR** subject to tamponade – retroperitoneal space, intracranial
4. **ACCUMULATION OF BLOOD IN BODY CAVITIES:** hemothorax, hemopericardium, hemarthrosis, hemoperitoneum

BLEEDING: active process that results in hemorrhage

BLEEDING DIATHESIS: increased tendency for severe bleeding, even in response to insignificant injury because of *deficits in the normal clotting mechanism*

CLOT: a hemostatic plug initiated as a normal physiologic response to vascular injury that increases in size sufficient to restore hemostasis & then is gradually removed to restore vascular integrity

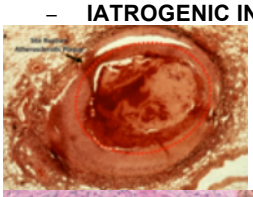
THROMBUS: a thrombus results from an initially physiologic clot (functioning to restore homeostasis) & then progressively becomes larger than required for its physiologic role as a hemostatic plug

- Alters/impedes normal blood flow from slight decrease to complete obstruction
- May undergo fragmentation with intravascular spread of fragments to another vascular site (**embolization**)

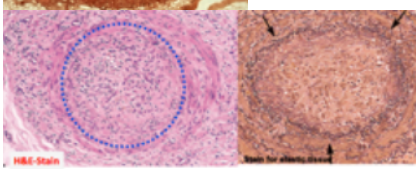
BODY SITE	TYPE
Artery	Thrombus
Cardiac chamber/aorta	Mural thrombus
Cardiac valve leaflet/cusp	Vegetations
Intravascular, arterioles	Microthrombi
Vein	Thrombus

1. THROMBOSIS: MUSCULAR MEDIUM & SMALL ARTERIES

- **SIZE**: millimeters
- **COMMON SITES:** coronary, cerebral, & femoral arteries
- Occur at ***sites of endothelial injury or turbulence*** with vast majority in *association with rupture of atherosclerotic plaque*; rare causes are endothelial injury secondary to vasculitis or trauma
- Retrograde propagation – *against direction of blood flow*
- **COMPLICATIONS:** partial obstruction of arterial blood flow (**tissue ischemia**) or vessel occlusion with cessation of blood flow (**infarction**)
  - *i.e.* ***myocardial infarction (MI), stroke (CVA)***
- **OUTCOMES**: (1) complete removal of thrombus, (2) thrombus partially obstructs & then permanently narrows lumen, (3) thrombus completely obliterates lumen
- **IATROGENIC INTERVENTIONS:** (1) IV fibrinolysis: streptokinase, (2) angioplasty with stent, (3) bypass



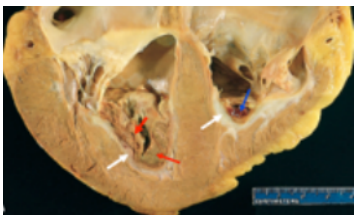
Thrombosis of Coronary Artery: Muscular Small Artery – arrow is pointing to site of rupture of atherosclerotic plaque



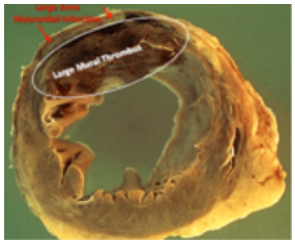
Thrombosis of Coronary Artery: Muscular Small Artery – Original lumen outlined in blue circle (left) & arrows pointing to internal elastic lamina (right). Lumen obliterated by organized thrombus with small recanalized vascular channels.

2. MURAL THROMBUS

- **Large** thrombus that adheres to luminal surface of large arteries – walls of cardiac chambers, along aorta within an aneurysm, or over a very large atherosclerotic plaque
- **PREDISPOSING CONDITIONS:** surface of necrotic endocardium or myocardium, zones of inactive myocardium (*infarction with fibrosis*) or stasis (***atrium with a-fib***)
- **GROSS APPEARANCE:** "mass" appearance; broad, thick shape that may exhibit **Lines of Zahn** – *alternating pale pink bands (platelets + fibrin) with layered zones of red cells; Lines of Zahn are submacroscopic & seen only in a **large thrombus!***

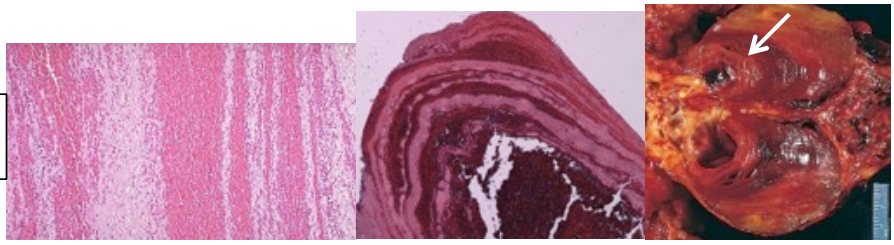


Mural Thrombus – red arrows are pointing to mural thrombus on the left & blue arrows are pointing to mural thrombus on the right ventricular apices over a white fibrous scar (white arrows).



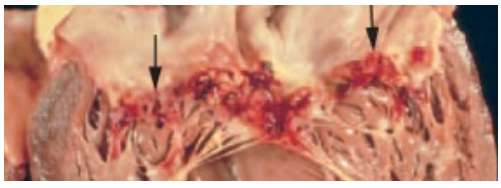
Mural Thrombus Overlying Large Acute MI – red arrows are pointing to the large zone of a myocardial infarction; the white circle encapsulates the large mural thrombus

Laminated Mural Thrombus in Aneurysm – Lines of Zahn



3. THROMBUS: VEGETATIONS

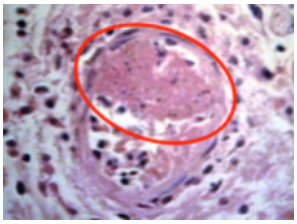
- Occur on cardiac valve cusps or leaflets
- Infective endocarditis (bacterial or fungal) is the most common cause & may lead to extensive erosion of valve leaflets/endocardium → triggers clot formation
- Appear as *irregular nodules* ("vegetations") that contain an admixture of clot & infectious agents
- ***Vegetations fragment into small pieces that become systemic emboli***



Vegetation of Mitral Valve – *Strep. Viridans;* large, friable vegetations

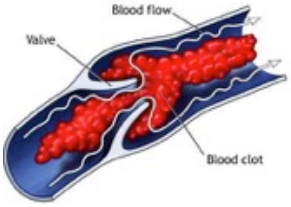
4. THROMBUS: MICROTHROMBI

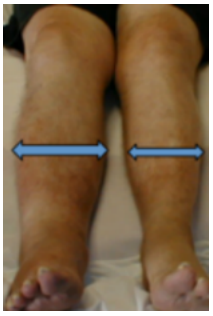
- Very small in size
- Formed in circulating blood, are NOT attached to vessel walls; present throughout the entire vascular volume
- **PATHOLOGIC SEQUELLAE:** they can lodge into & partially obstruct small arterioles
- **ASSOCIATED CLINICAL DISEASES:** Disseminated Intravascular Coagulation (DIC) & Thrombotic Thrombocytic Purpura (TTP) – *more on these diseases later*



5. DEEP VEIN THROMBOSIS (DVT)

- Typically large, centimeters
- Occur in zones of **stasis** (distal to closed valves);
- DVTs of **iliac, popliteal**, tibial & femoral account for 95% thromboemboli
- Anterograde – *propagates blood flow toward heart*
- POTENTIAL OUTCOMES: (1) resolution, (2) embolize to lungs, (3) incorporate into wall, (4) organize/recanalize
- **MAJOR COMPLICATIONS:**
  - Nearly half of episodes of DVT are clinically asymptomatic
  - **EDEMA** – numerous collateral routes allow flow around a venous obstruction; *edema only results after substantial narrowing or obstruction of the largest deep veins*
  - **THROMBOEMBOLUS**: **Pulmonary Embolism (PE) – *most likely site of origin: iliac & popliteal veins***





Venous Obstruction by DVT in R Iliac Vein → Increased Hydrostatic Pressure:
Asymmetric right leg

EMBOLISM: sudden blockage of an artery by a clot or foreign body that has moved to its site of lodgment via blood flow from another body location

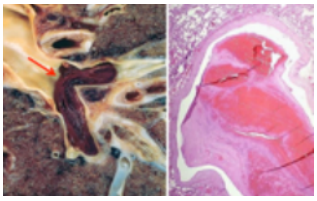
EMBOLUS: detached intravascular mass carried by the blood to a site distant from its point of origin

THROMBOEMBOLUS: when a detached portion of thrombus moves through the vascular system

TYPE	MECHANISM
PULMONARY EMBOLISM	Travels in **venous** system & lodges in pulmonary arterial system Origin is from **DVT** or thrombus on walls/valves of **right-sided cardiac chamber**
SYSTEMIC EMBOLISM	Travels & lodges in systemic arterial distribution of aorta Origin from a thrombus on walls/valves of **left-sided cardiac chamber**
FAT EMBOLISM	Multiple fat emboli from bone marrow travel via vascular system to brain microvasculature
AMNIOTIC FLUID EMBOLISM	Amniotic fluid during parturition enters **venous** system → shock, respiratory arrests, DIC

1. PULMONARY (THROMBOEMBOLUS) EMBOLISM

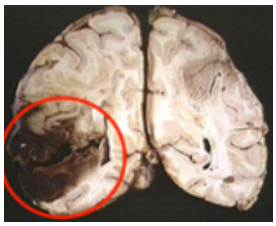
- Embolus travels within venous system
- 95% originate from DVT of LE
- **PATTERNS OF PE**:
  - Single large mass, "saddle embolus," obstructing one/both main pulmonary arteries, usually fatal
  - Multiple sequential emboli
  - Multiple near simultaneous emboli or "showers"
  - MOST ARE CLINICALLY SILENT
- **IMMEDATE FATAL OUTCOME** results when obstruction by embolus of **50-60%** or greater than pulmonary artery inflow into pulmonary circulation
- **CLINICAL SIGNS & SYMPTOMS**: abrupt onset, acute SOB, tachypnea, dyspnea, unilateral sharp chest pain on inspiration; patient with hx of 1 PE at much greater risk for reoccurrence
  - There has been a dramatic decrease in PE incidence, most likely due to shorter post-op bed rest periods & widespread use of anticoags in hospitalized patients



Large Thromboemolus from LE Thrombus – lodges & obstructs a pulmonary artery branch bifurcation

2. SYSTEMIC (THROMBOEMBOLUS) EMBOLUS

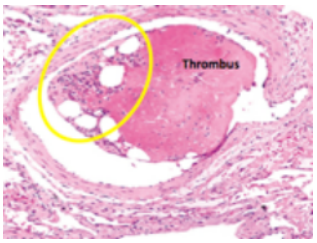
- Embolus travels within arterial (systemic) circulation
- 80% originate from mural thrombus in a cardiac chamber: 2/3 from thrombus overlying an area of MI & 1/3 form thrombus in dilated/fibrillating left atrium
- **MAJOR INFARCTION SITES**: 75% lower extremities, 10% brain



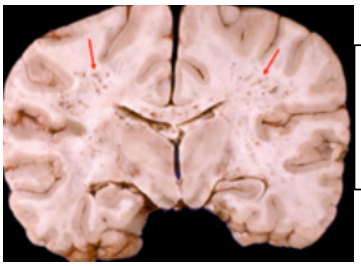
SYSTEMIC EMBOLUS – Brain Infarction following embolus from left-sided ventricular wall mural thrombus

3. FAT EMBOLISM

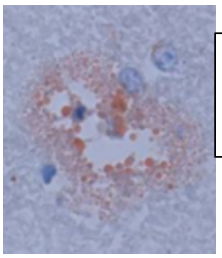
- Forms following fracture of long bones (**femur & tibia**)
- Acute onset but occurs **4-7 days post-injury!**
- **CLINICAL SIGNS & SYMPTOMS:** neurologic symptoms (LOC due to "brain purpura"), pulmonary insufficiency, anemia, thrombocytopenia (DIC), **skin petechiae** in 50% of patients; **10% fatality rate!**
- *Most common in pulmonary vasculature after fractures of long bones, burns, or vigorous CPR*



Fat Embolism – bone marrow embolus in pulmonary circulation; cellular elements (yellow) on L side embolus are hematopoietic cells -- clear vacuoles represent marrow fat. Relatively uniform red area on R of embolus is **early organizing thrombus.**



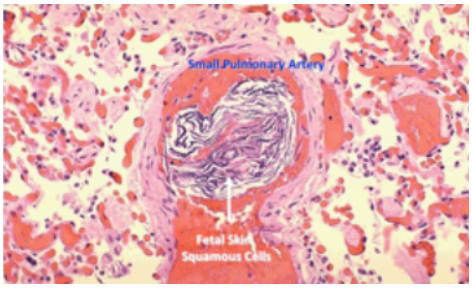
Fat Embolism – **numerous petechial hemorrhages** results from fat emboli to microvasculature of brain (particularly in white matter); edema may cause herniation



Fat Embolism – Oil red O stain of *peripheral cerebral artery branch* revealing numerous globules of lipid

4. AMNIOTIC FLUID EMBOLISM (AFE)

- *Now the leading cause of obstetrical deaths during delivery*
  - 60% maternal mortality rate for AFE
- *Complication of labor & immediately follows birth due to amniotic fluid in maternal circulation*
- Dramatic & sudden! – **15 to 120 seconds** duration from stable status (normal delivery) until presence of catastrophic clinical findings
- **CLINICAL SIGNS & SYMPTOMS:** severe dyspnea, cyanosis, profound shock, respiratory arrest, sudden death
- Patients that survive the initial severe acute respiratory syndrome develop severe DIC & shock lung – **diffuse alveolar damage**
  - 85% of survivors have permanent hypoxia-induced neurologic damage



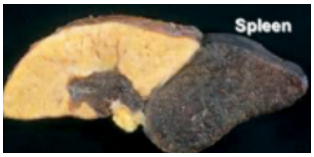
Amniotic Fluid Embolism – amniotic fluid gains access to uterine veins following a tear in the placental membranes; amniotic fluid contents (fetal epithelial, lanugo hair, vernix) diffusely lodge in small pulmonary arteries, causing severe dyspnea & hypoxia.
White arrow pointing to fetal skin squamous cells.

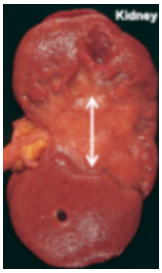
INFARCTION – INFARCT: zone of tissue ischemic necrosis caused by *occlusion of arterial supply (white, anemic infarct) or distension with venous blood (red, hemorrhagic infarct)*

- 99% infarctions are caused by thrombotic or embolic events
- HISTOLOGY: **Coagulative necrosis**, *except in brain → **liquefactive necrosis***
- *Myocardial infarction (MI) & brain infarction (stroke – CVA)*

1. WHITE [ANEMIC] INFARCTION: ARTERIAL OCCLUSION

- Occurs after occlusion of arterial blood flow to single-end artery tissue in "solid" organ (i.e. brain, heart, extremity, spleen, & kidney)

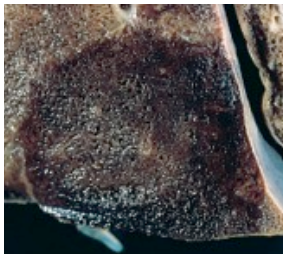




White Infarction – pale "white" appearance (grossly) as hemorrhage is cleared; margins sharply defined; non-viable tissue replaced with dense fibrous scar (seen on kidney image – R)

2. RED [HEMORRHAGIC] INFARCTION

- The tissue is *plugged up or crammed with venous blood* that remains in the tissue & prevents further inflow, leading to ischemic necrosis of the tissue parenchyma
- Far less common that white infarcts & on average, are small (except testicular torsion)
- Rarely fatal
- VARIOUS ETIOLOGIES:
  - **VENOUS OBSTRUCTION (OCCLUSION):** ovarian or testicular torsion
  - **VENOUS OBSTRUCTION (PARTIAL):** prolonged venous congestion
  - **DUAL BLOOD SUPPLY:** lung infarction
  - **REPERFUSION INJURY**: re-perfusion event following recent ischemic infarct



Red Infarction: DUAL BLOOD SUPPLY – red wedge-shaped pulmonary infarct secondary to a thromboembolus lodging in a medium-sized pulmonary artery

Red Infarction: OCCLUSION VENOUS RETURN – torsion of the spermatic cord leading to hemorrhagic infarction of the testis

SHOCK: CARDIOVASCULAR COLLAPSE

- *A state of diminished cardiac output or reduced effective blood volume resulting in systemic hypotension, which results in impaired tissue perfusion & cellular hypoxia*
- ***Sine Qua Non:*** **Hypotension** with markedly decreased blood pressure of diastolic <40 & pulse pressure <20
- **CLINICAL SIGNS&SYMPTOMS:** hypotensive, weak rapid pulse, tachypnea, cool/clammy cyanotic skin, "tilt test"
- A MEDICAL EMERGENCY!

TYPE OF SHOCK	CLINICAL EXAMPLE	PRINCIPAL MECHANISMS
CARDIOGENIC	Myocardial infarction Ventricular rupture Arrhythmia Cardiac tamponade Pulmonary embolism	Failure of myocardial pump resulting from intrinsic myocardial damage, extrinsic compression, or obstruction to outflow *Pt presents with hypotension, weak, rapid pulse, tachypnea, cool/clammy skin.*
HYPOVOLEMIC	Fluid loss *Hemorrhage, vomiting, diarrhea, burns, or trauma* ***(car accident)***	Inadequate blood or plasma volume *Pt presents with hypotension, weak, rapid pulse, tachypnea, cool/clammy skin.*
SHOCK ASSOCIATED WITH SYSTEMIC INFLAMMATION – SEPTIC SHOCK	Overwhelming microbial infections (bacterial & fungal) [Gram Neg Septicemia – LPS] Superantigens (i.e. TSS) Trauma, burns, pancreatitis	Activation of cytokine cascades by high levels of endotoxin; peripheral vasodilation & pooling of blood; endothelial activation/injury; leukocyte-induced damage; DIC *Pt's skin may initially be warm & flushed because of peripheral vasodilation.*
NEUROGENIC	*Brain or spinal injury*	*Loss of sympathetic stimulation to blood vessels resulting in vasodilation (blood pooling away from the heart) & sudden onset of hypotension due to decreased peripheral vascular resistance*
ANAPHYLACTIC	*Allergic rxn (Type I HSR –* ***IgE****)* *Peanuts, antibiotics, bee stings*	*Allergic reaction to outside chemical/substance activates excessive immune response resulting in multiple organ system failure; mast cells/basophils leak histamine affecting muscles of lung, heart, & blood vessels → decreased blood flow & O_2 supply to cells in the body → shock*

STAGES OF SHOCK

1. **Non-progressive Phase:** *physiologic compensatory mechanisms* allow for continued function of vital organs
   - **CLINICAL FINDINGS**: hypotension, tachycardia (rapid HR), tachypnea (rapid breathing), peripheral vasoconstriction resulting in cool, clammy cyanotic skin, renal conservation of fluids (oliguria)
   - *The 1st phase is when diagnosis of shock can be missed. If you do not clinically suspect shock, you may miss the diagnosis. Closely observe any patients with signs of* ***significant bleeding*** ***(hemorrhage → hypovolemic shock).***
2. **Progressive Phase:** continued *tissue hypoperfusion* results in onset of worsening circulatory & *metabolic imbalances* with development of metabolic *acidosis* (secondary to ischemia)
   - **CLINICAL FINDINGS**: peripheral vascular pooling, ischemic encephalopathy – *patient confused & delirious*, acute tubular necrosis (renal insufficiency – decreased UO, acute renal failure)
   - **Late Progressive Phase:** DIC, hemorrhagic enteropathy, shock lung, adrenal hemorrhage
3. **Irreversible Phase:** tissue injury & damage is so great that *recovery is not possible*

SEPTIC SHOCK – Microbial products (i.e. gram neg LPS) activate endothelial cells and cellular & humoral elements of innate immune system, initiated a cascade of events that lead to end-stage multiorgan failure. *High levels of endotoxin result in production of TNF, IL-1, IL-6, & IL-8. (IL-6 is the most potent activator of acute phase response.) Cytokines trigger profound vasodilation & hypotension.*