



# Boards & Beyond: Pathology Slides

Color slides for USMLE Step 1 preparation  
from the Boards and Beyond Website

Jason Ryan, MD, MPH

2022 Edition

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# Cellular Adaptations

## Cellular Adaptations

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## Cellular Response to Stress

- Stressors
  - Pathologic: ischemia
  - Physiologic: pregnancy
- Adaptation
  - Reversible change in response to stress
- Injury
  - Reversible → irreversible
- Cell death



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## Cellular Adaptations

- Hypertrophy
  - Increase in cell size
- Hyperplasia
  - Increase in cell number
  - Often occurs with hypertrophy
- Atrophy
  - Decrease in cell size
- Metaplasia
  - Change in phenotype

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## Hypertrophy

- Increase in **cell size**
  - More proteins, filaments
- May occur together with hyperplasia
- **Muscle tissue:** hypertrophy with more workload



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## Hypertrophy

- Physiologic examples
  - Body builders (muscle hypertrophy for use)
  - Uterus in pregnancy (hormone driven)
- Pathologic example:
  - Left ventricular hypertrophy
  - Response to hypertension or increased workload



Øyvind Holmstad/Wikipedia



Patrick Lynch/Wikipedia

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## Hyperplasia

- Increase in **cell number**
- Often due to excess hormone stimulation
- Physiologic or pathologic
- Often accompanied by hypertrophy

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## Physiologic Hyperplasia

- **Breast growth** at puberty
  - Hyperplasia and hypertrophy of glandular epithelial cells
- **Liver regeneration**
  - Partial liver donation → liver grows back to full size
  - Hyperplasia of remaining hepatocytes
- **Bone marrow**
  - Anemia → hyperplasia of red cell precursors
  - Red blood cell production may increase by 8x



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## Pathologic Hyperplasia

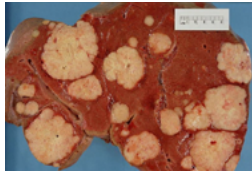
- **Endometrial hyperplasia**
  - Growth due to **estrogen**
- Prostatic hyperplasia
  - Excessive response to **androgens**
- Human papilloma virus
  - Skin warts (epidermal hyperplasia)
  - Genital warts (mucosal hyperplasia)



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## Malignancy

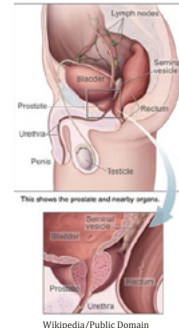
- **Often develops from hyperplasia**
- Increased cell division
- More chances for error in cell cycle control
- Uncontrolled growth



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## Benign Prostatic Hyperplasia

- Pathologic hyperplasia
- Does not lead to malignancy



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## Hypertrophy vs. Hyperplasia

- Permanent/non-dividing cells
  - Myocytes, skeletal muscle cells, nerves
  - Permanent G<sub>0</sub> state ("terminally differentiated")
  - Hypertrophy
- Cells capable of growth/division
  - Epithelial cells (GI tract, breast ducts, skin)
  - Commonly undergo hyperplasia
  - May lead to dysplasia/cancer

## Atrophy

- **Reduction in size** of organ/tissue
- Decrease in cell size and/or number of cells
- Physiologic examples:
  - Embryonic structures (notochord)
  - Uterus after childbirth (loss of hormone stimulation)
  - Breast/uterus at menopause



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## Pathologic Atrophy

- **Unused skeletal muscle**
  - Bed rest
  - Immobilization (cast after fracture)
- Cachexia
  - Poor nutrition
- Decreased blood supply
  - Senile atrophy of brain (atherosclerosis)
- Loss of innervation
  - Neuromuscular disorders



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## Atrophy Mechanisms

- **Ubiquitin-proteasome pathway**
  - Proteins tagged by ubiquitin
  - Transported to proteasomes for degradation
  - Stressors may activate ligases that attach ubiquitin
- **Autophagy**
  - "Self eating"
  - Cellular components fused with lysosomes

## Metaplasia

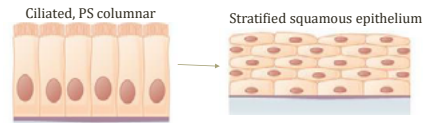
- **Change in cell type** to adapt to stress
- New cell type able to withstand stress
- Commonly from one **epithelial cell** type to another
- Potentially reversible
- Can lead to dysplasia/malignancy

## Metaplasia

- Respiratory tract in **smokers**
  - Normal columnar epithelium in trachea/bronchi
  - Changes to squamous epithelium (most common metaplasia)
  - Squamous epithelium more durable
  - Loss of cilia → more vulnerable to infections

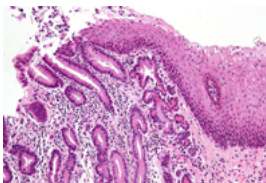


Pixabay/Public Domain



## Metaplasia

- **Barrett's esophagus**
  - Gastric acid (stressor) in esophagus
  - Normal stratified squamous epithelium
  - Changes to columnar epithelium (intestines)



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## Metaplasia

- **Myositis Ossificans** (heterotopic ossification)
  - *Muscle* metaplasia to bone (**not epithelial cells**)
  - Mesenchymal cells → osteoblastic tissue
  - Forms lamellar bone in muscles
  - Follows trauma (hip arthroplasty)
  - Muscles become stiff



Tdvorak/Wikipedia

## Vitamin A Deficiency

- Important for maintaining epithelial cells
- Deficiency: epithelial metaplasia and keratinization
- **Upper respiratory tract**
  - Epithelial metaplasia
  - Epithelium replaced by keratinizing squamous cells
  - Abnormal epithelium → pulmonary infections
- **Xerophthalmia (dry eyes)**
  - Normal epithelium secretes mucus
  - Replaced by keratinized epithelial cells

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## Apocrine Metaplasia

- Form of **fibrocystic change** in breast
- Also called “benign epithelial alteration”
- Alterations to lobular epithelial cells
- Take on appearance of apocrine (gland) cells
- *Does not* lead to dysplasia/cancer

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## Dysplasia

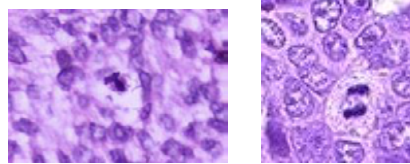
- **Disordered proliferation**
- Non-neoplastic but can be pre-cancerous
  - Mild dysplasia may resolve
  - Severe dysplasia may be irreversible → cancer
- Usually occurs in epithelial tissues
- Usually preceded by **hyperplasia or metaplasia**



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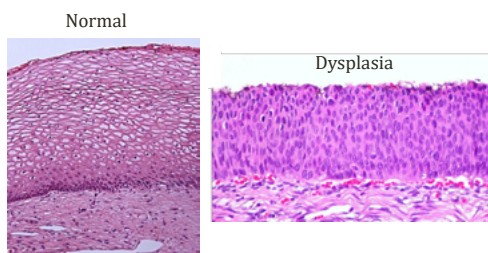
## Dysplasia

- Pleomorphism
- Abnormal nuclei (hyperchromatic, large)
- Mitotic figures (clumped chromatin)



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## Cervical Dysplasia



Ed Uthman/Wikipedia

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# Cellular Injury

## Cellular Injury

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## Cell Injury

- Four general causes of cell injury
  - Capacity for adaptation exceeded
  - Exposure to toxic/injurious agents
  - Deprived of nutrients
  - Mutation disrupts metabolism
- Reversible to a point
- Severe or persistent injury may be irreversible
- May lead to cell death



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## Cell Death

- Two ways cells die:
  - Necrosis: **inflammatory** process
  - Apoptosis: **non-inflammatory**
- Necrosis preceded by classic cellular changes
  - Reversible changes → irreversible changes

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## Reversible Cell Injury

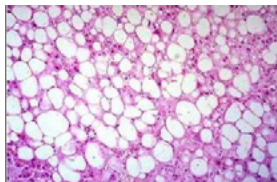
- **Cellular swelling**
  - Major feature of most forms of reversible injury
  - Hydropic change = water accumulation in cell
  - Hard to see under microscope
  - ↓ Na/K ATPase pumps



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## Reversible Cell Injury

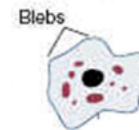
- **Fatty change**
  - Seen only in systems that heavily metabolize fatty acids
  - Liver, heart, skeletal muscle
  - Lipid vacuoles appear in cytoplasm



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## Reversible Cell Injury

- Mitochondrial swelling
- **Membrane blebbing**
  - Disruption of cytoskeleton
- Dilation of **endoplasmic reticulum**
  - Ribosomes detach from ER
  - ↓ protein synthesis
  - "Polysomal detachment"
  - Polysome = cluster of ribosomes



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## Irreversible Cell Injury

Necrosis

- **Membrane damage**
  - Contents leak
  - Causes inflammation
  - Serum detection of cell contents (troponin, lipase)
  - Calcium-dependent phospholipases
- **Rupture of lysosomes**
  - Enzymes degrade cellular contents

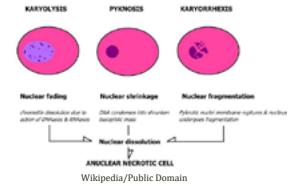


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## Irreversible Cell Injury

Classic Nuclear Changes

- Karyolysis (loss of basophilic/dark color)
- Pyknosis (nuclear shrinkage)
- Karyorrhexis (fragmented nucleus)



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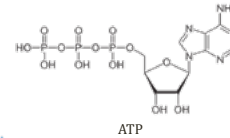
## Mechanisms of Injury

- ATP depletion
- Calcium
- Mitochondrial damage
- Free radicals

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## ATP Depletion

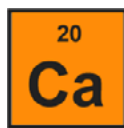
- Many causes
  - **↓ oxygen supply**
  - Mitochondrial damage
  - Direct effect some toxins
- Loss of membrane pumps
- Loss of protein synthesis



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## Calcium

- Normally very low compared with outside cell
- **Calcium influx: hallmark of injury**
  - Released from intracellular storage
  - Influx across cell membrane
- Causes cellular injury
- **Calcium-dependent phospholipases**
  - Activated by increased calcium
  - Breakdown of membrane phospholipids
- Damages mitochondria



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## Mitochondrial Damage

- Lack of oxygen
- Reactive oxygen species
- **Mitochondrial permeability transition pore**
  - Opened by **calcium**
  - Loss of membrane potential
  - Failure of oxidative phosphorylation



Blaussen gallery 2014\*. Wikiversity Journal of Medicine

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# Free Radicals

## Free Radicals

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## Mechanisms of Injury

- ATP depletion
- Calcium
- Mitochondrial damage
- Free radicals

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## Vocabulary

- **Free radical**
  - Single, unpaired electron in outer orbit
  - Highly reactive
  - May damage many cellular components
- **Reactive oxygen species**
  - Oxygen free radicals
  - Several forms
  - Superoxide ( $O_2^-$ )
  - Hydrogen peroxide ( $H_2O_2$ )
  - Hydroxyl radical ( $OH^\cdot$ )

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## Free Radicals

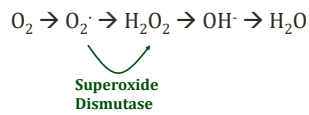
- Generated in cells under normal conditions
- Inactivated in cells
- Cell maintain low level under normal conditions
- High level  $\rightarrow$  cell injury



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## Free Radical Generation

- Normal metabolism involving oxygen
- **Oxidative phosphorylation**
  - Yields small levels of superoxide ( $O_2^-$ )
  - Converted to  $H_2O_2$  by superoxide dismutase
  - $H_2O_2$  more stable and can cross membranes
  - Converted to  $H_2O$



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## Free Radical Generation

- Radiation (UV light, X-rays)
- Mechanism of **radiation therapy for cancer**
- Metabolism of drugs
- Transition metals
- Respiratory burst

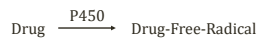


Dina Wakulchik/Wikipedia

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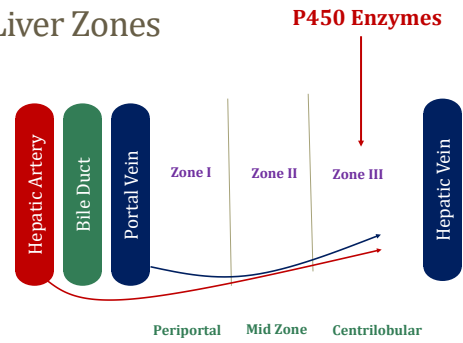
## Drug Metabolism

- Phase 1: drug modification
- Phase 2: conjugation
- Phase 3: additional modification and excretion
- **Cytochrome P450 enzymes**
  - Smooth ER in liver
  - Part of **phase 1 metabolism**
  - Generate "bioactive intermediates" (free radicals)



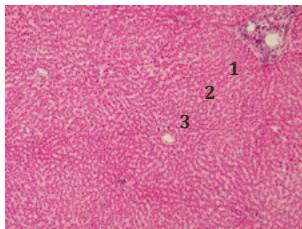
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## Liver Zones



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## Liver Lobules



Reytan / Wikipedia

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## Acetaminophen

Tylenol

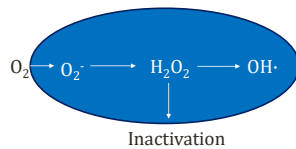
- Metabolized in liver to NAPQI
  - N-acetyl-p-benzoquinone imine
- **NAPQI** is a reactive oxygen species (ROS)
- Causes free radical liver damage



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## Transition Metals

- Superoxide ( $\text{O}_2^-$ ) converted to  $\text{H}_2\text{O}_2$  for inactivation
- Fenton Reaction forms hydroxyl radical ( $\text{OH}\cdot$ )
  - $\text{H}_2\text{O}_2 + \text{Fe}^{2+} \rightarrow \text{Fe}^{3+} + \text{OH}\cdot$
  - $\text{H}_2\text{O}_2 + \text{Cu}^+ \rightarrow \text{Cu}^{2+} + \text{OH}\cdot$
- **Hemochromatosis/Wilson's**
  - Iron and copper toxicity



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## Transition Metals

- Metal storage and transport proteins:
  - Transferrin/Ferritin/Lactoferrin (Fe)
  - Ceruloplasmin (Cu)



Tomihahndorf

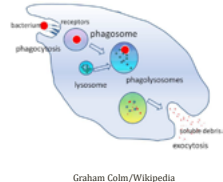


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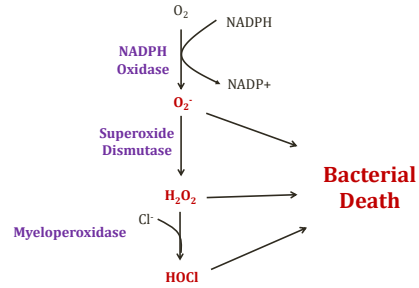
## Respiratory Burst

- Phagocytes engulf bacteria in phagosome
- **Generate  $H_2O_2$**  in phagosome to kill bacteria
- Uses three key enzymes:
  - NADPH oxidase
  - Superoxide dismutase
  - Myeloperoxidase



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## Respiratory Burst



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## Free Radical Inactivation

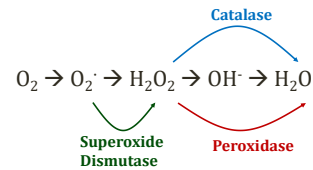
- Spontaneous decay
- **Antioxidants**
  - Free radical scavengers
  - Vitamin E, A, C, glutathione



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## Free Radical Inactivation

- **Enzymes**
  - Catalase (peroxisomes)
  - Superoxide dismutase (mitochondria)
  - Glutathione peroxidase (cytoplasm of cells)
    - Requires glutathione:  $GSH + H_2O_2 \rightarrow H_2O$



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## CGD

Chronic Granulomatous Disease

- Loss of function of NADPH oxidase
- Phagocytes cannot generate  $H_2O_2$
- **Catalase (+) bacteria** breakdown  $H_2O_2$ 
  - Host cells have no  $H_2O_2$  to use  $\rightarrow$  recurrent infections
- Catalase (-) bacteria generate their own  $H_2O_2$ 
  - Phagocytes use despite enzyme deficiency
- Five organisms cause almost all CGD infections:
  - Staph aureus, Pseudomonas, Serratia, Nocardia, Aspergillus

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Source: UpToDate

## G6PD Deficiency

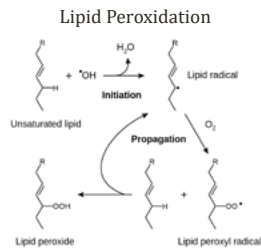
- Limited supply of **glutathione**
- RBC damage by free radicals  $\rightarrow$  hemolysis
- Classic trigger: fava beans
  - Contain vicine
  - Converted to divicine  $\rightarrow$  ROS
  - Depletes glutathione



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## Free Radical Cell Damage

- **Peroxidation of lipids**
  - Peroxide: O-O
  - Damages membranes
- Oxidation of proteins
  - Damage enzymes
- Disruption of DNA
  - Breaks, crosslinking



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## Reperfusion Injury

- Myocardial infarction  $\rightarrow$   $\downarrow$  blood flow (ischemia)
- Reperfusion  $\rightarrow$   $\uparrow$  blood flow
  - Some reversibly injured cells recover (good)
  - Some cells damaged by reperfusion (bad - paradoxical)
- Several mechanisms
- $\uparrow$  oxygen supply  $\rightarrow$  **generation of free radicals**
  - Antioxidants lost from injury
  - Damaged mitochondria incompletely reduce oxygen

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## Carbon Tetrachloride

$\text{CCl}_4$

- Industrial solvent
- Historically used for dry cleaning
- Liver highly sensitive to damage
- Converted to  $\text{CCl}_3$  free radical (CYP450 enzymes)
  - Lipid peroxidation
  - Inhibition of lipoprotein synthesis/secretion
  - Accumulation of lipids
- Result: **fatty liver**

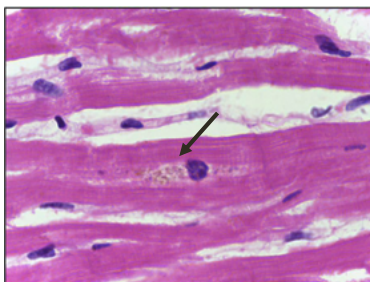
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## Lipofuscin

- Insoluble cellular pigment
- Yellow-brown color
- Contain **oxidized lipids**
- Thought to be derived from lipid peroxidation
- Accumulates over time in lysosomes
- Not pathological
- Seen with **aging**

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## Lipofuscin



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# Apoptosis

## Apoptosis

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## Apoptosis

- **Programmed cell death**
- Cell activates its own enzymes to destroy cell
- Membrane remains intact
- **No inflammation**
- Cell ultimately consumed by phagocytes



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## Apoptosis

- Active process
  - **ATP-dependent**
  - Contrast with necrosis
- Some stimuli cause **apoptosis and necrosis**
  - Example: myocardial ischemia
  - Evidence for both forms of cell death
  - Initial cellular response: apoptosis (avoids inflammation)
  - Later response: necrosis (ATP depleted)

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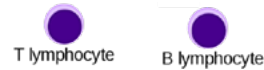
## Apoptosis

Causes

- Embryogenesis
- Hormone withdrawal
  - Occurs in hormone-dependent tissues
  - Endometrium with progesterone withdrawal
- Immune cells
  - T-cells in thymus
  - B-cells in germinal centers
  - Death of self-reactive immune cells
  - Immune cells after inflammation resolves



Flickr/lunarc caustic

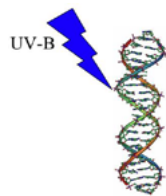


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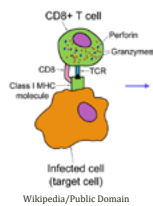
## Apoptosis

Causes

- DNA damaged cells
- Abnormal cells
- Infected cells (especially viral)



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## Apoptotic Mechanisms

- Caused by **caspase** enzymes
  - Inactive enzymes in cytosol
  - When activated → apoptosis
- Two “pathways” for caspase activation
- Intrinsic (mitochondrial) pathway
  - Initiated by mitochondria
- Extrinsic (death-receptor) pathway
  - Membrane death receptors activated

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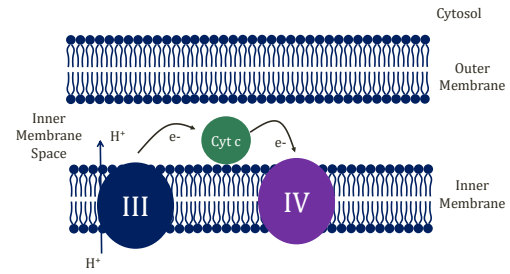
## Intrinsic Pathway

- Opening of mitochondrial membranes
- Release of **cytochrome c**
  - Binds to APAF-1 (apoptosis-activating factor)
  - Activation of caspases
- Controlled by BCL2 family of proteins
  - Some pro-apoptotic; some anti-apoptotic
  - Balance determines if cell undergoes apoptosis



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## Electron Transport



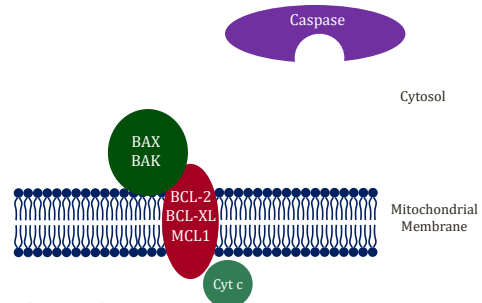
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## Intrinsic Pathway

- Many, many BCL2 family proteins
- Anti-apoptosis: **BCL-2, BCL-XL, MCL1** proteins
  - Found in mitochondrial membranes
  - Prevent cytochrome c from entering cytosol
- Pro-apoptosis: **BAX and BAK** proteins
  - Bind to anti-apoptotic proteins
  - Open pores in mitochondrial membranes
  - Promote apoptosis
- **As** are for Apoptosis

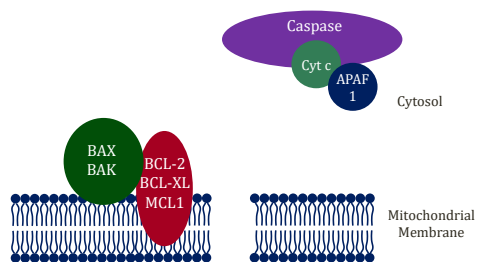
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## Intrinsic Pathway



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## Intrinsic Pathway



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## Follicular Lymphoma

- Subtype of non-Hodgkin lymphoma
- B-cell malignancy
- **Overexpression of BCL-2**
- Mitochondrial pores will not open
- Caspases cannot activate
- Cell will not undergo apoptosis
- Result: Uncontrolled cell growth

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## Intrinsic Pathway

### Triggers

- **Withdrawal of growth factor**
  - Hormones for hormone-sensitive tissue (uterus)
  - Cytokines for immune cells
  - Embryogenesis
- **DNA damage**
  - DNA damage (radiation, chemotherapy)
  - P53 can activate BAK and BAX
- **Abnormal proteins**
  - Caused by heat, hypoxia, low glucose

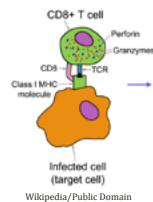
## Extrinsic Pathway

- **Death receptors**
  - All part of TNF family of receptors
  - Span plasma membrane into cytoplasm
- **FAS (CD95)**
  - Well-described death receptor found on many cells
  - Binds FAS-ligand
  - Triggers sequence that leads to activation of caspases

## CD8 T-cells

### Killing of virus infected cells

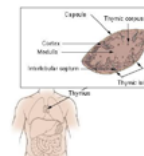
- Activated by presentation of foreign antigens (MHC1)
- Release perforin and granzymes
  - Lead to **activated caspases**
- Produce Fas ligand
  - Binds to Fas (CD95) on surface of cells



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## Extrinsic Pathway

- **Thymic medulla**
  - T-cells that bind to self-antigens die (negative selection)
  - Death occurs via extrinsic pathway
  - FAS-FAS-ligand interactions



Thymus  
Public Domain/Wikipedia

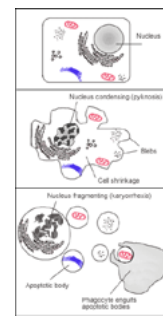
## Extrinsic Pathway

- **Autoimmune lymphoproliferative syndrome**
  - Defective FAS-FAS-ligand pathway for apoptosis
  - Poor negative selection (more T-cell survival)
  - Overproduction of lymphocytes
  - Lymphadenopathy, hepatomegaly, splenomegaly
  - High risk of lymphoma
  - Autoimmune diseases

## Apoptosis

### Cellular Changes

- Cell shrinkage
  - Contrast with necrosis/swelling
- Chromatin condensation
  - Pyknosis
  - Hallmark of apoptosis

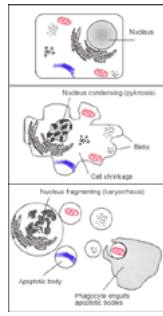


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# Apoptosis

## Cellular Changes

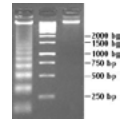
- Membrane blebbing
- Formation apoptotic bodies
  - Membrane fragments
  - Cell organelles
  - Ligands for phagocyte receptors
  - Consumed by phagocytosis



Wikipedia/Public Domain

# DNA Laddering

- Apoptotic caspases cleave DNA at specific regions
- Forms pieces in multiples of 180-185 kbp
- Forms a "ladder" of sizes on gel electrophoresis
- Necrosis: random fragments



# Apoptosis and Necrosis

Apoptosis	Necrosis
<b>Non-inflammatory</b>	<b>Inflammatory</b>
<b>Cell shrinkage</b>	<b>Cell Swelling</b>
<b>Membrane blebs</b>	<b>Membrane damage</b>
<b>Intact Membrane</b>	<b>Many cells affected</b>
<b>Single cell effected</b>	<b>No laddering</b>
<b>DNA laddering</b>	<b>Always pathological</b>
<b>Can be physiologic</b>	

# Necrosis

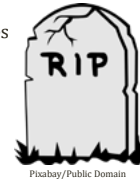
## Necrosis

Jason Ryan, MD, MPH

Boards&Beyond

## Necrosis

- Form of cell death
- Cell membrane loss
- Leakage of cellular contents
- Elicits inflammatory response
- Affects tissue beds
- Results in gross and microscopic changes



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## Necrosis

- Two major types
  - Coagulative
  - Liquefactive
- Other types
  - Caseous
  - Fibrinoid
  - Fat
  - Gangrenous



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## Coagulative Necrosis

- Preservation of tissue architecture for days
- Injury damages cells **and enzymes**
  - Major difference from liquefactive necrosis
  - Loss of enzymes **limits proteolysis**
  - Tissue architecture remains intact for days
- Phagocytosis of cell remnants (takes time)

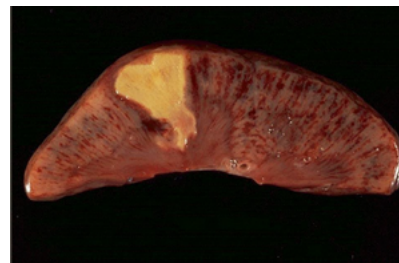
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## Coagulative Necrosis

- Gross: tissue becomes firm
- Microscopic:
  - Architecture preserved
  - Cell nuclei lost
  - Red/pink color on H&E stain (cell takes up more stain)
  - Inflammatory cells

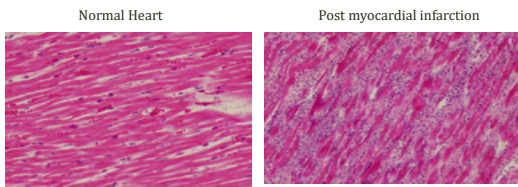
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## Coagulative Necrosis



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## Coagulative Necrosis

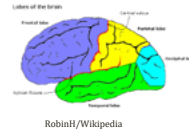


Ryan Johnson/Flickr

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## Coagulative Necrosis

- Seen with **infarctions and ischemia**
  - Myocardium
  - Kidney
  - Spleen
- Key exception: **brain** (liquefactive necrosis)



RobinnH/Wikipedia

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## Liquefactive Necrosis

- Abscesses (bacterial/fungal) and brain infarctions
  - Cause in brain infarctions poorly understood
- Infection draws inflammatory cells
- Tissue is "liquefied" into thick, liquid mass
- Enzymes from microbes
- Enzymes from lysosomes of dying cells

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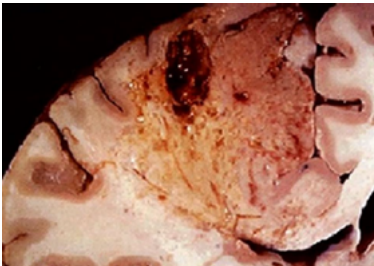
## Liquefactive Necrosis

- Gross: liquid/pus or abscess cavity
- Microscopic: numerous neutrophils

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## Liquefactive Necrosis

Brain after stroke

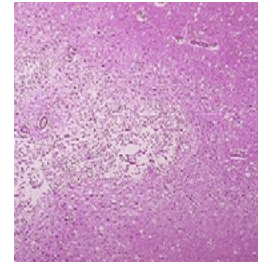


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## Liquefactive Necrosis

Brain after stroke



R. Geetha/Slideshare

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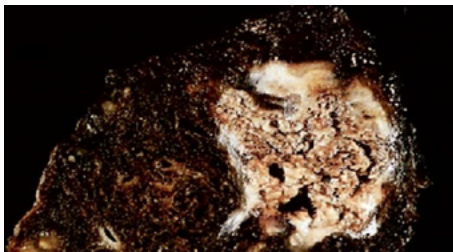
## Caseous Necrosis

- “Cheese like”
- Rarely occurs outside of tuberculosis infection
- Mycobacteria resist digestion
- Macrophages form giant cells
- Slow breakdown of infection
- **Mycolic acid** and lipids give cheese-like appearance

## Caseous Necrosis

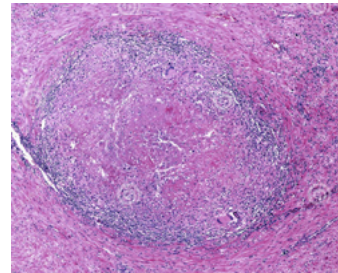
- Gross: Cheesy-like (caseating) substance
- Microscopic: granulomatous inflammation
  - Necrotic center
  - Ring of lymphocytes and macrophages
  - Epithelioid cells
  - Giant cells (fused activated macrophages)

## Caseous Necrosis



Wikipedia/Public Domain

## Caseous Necrosis



Public Domain

## Fat Necrosis

- Necrosis of fat
- Classic example: **acute pancreatitis**
  - Cause: **lipases** released from pancreatic cells
  - Breakdown of peritoneal fat
  - Fatty acids combine with calcium (saponification)
  - “Chalky-white” tissue

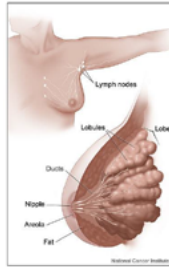
## Fat Necrosis



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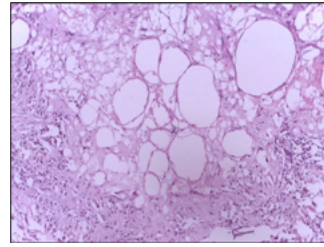
## Fat Necrosis

- Fat necrosis of breast
  - Results from **trauma**
  - Often biopsy, surgery
  - Sports injury, seatbelt injury
  - Can mimic breast cancer



Wikipedia/Public Domain

## Fat Necrosis



Wikipedia/Public Domain

## Gangrenous Necrosis

- Subtype of coagulative necrosis
- Caused by ischemia
- Lost blood supply to **limbs** or **bowel**
- Multiple tissue layers involved
- Dry gangrene: dry, black, shrunken tissue
- Wet gangrene:
  - Superimposed bacterial infection
  - Coagulative and liquefactive necrosis
  - Moist, soft, swollen
  - Pus, foul smelling

## Dry Gangrene



James Hellman, MD/Wikipedia

## Wet Gangrene

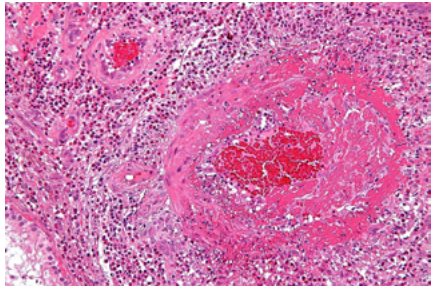


S Anand/Slideshare

## Fibrinoid Necrosis

- Occurs in **blood vessels**
- Only visible under microscope (no gross findings)
- Occurs in **autoimmune disorders**
  - Antibody-antigen complexes deposit in vessel walls
  - Type III hypersensitivity reaction
- Fibrin leaks into vessel wall (pink on microscopy)

## Fibrinoid Necrosis



Nephron/Wikipedia

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## Fibrinoid Necrosis

- Classic disorder: **polyarteritis nodosa**
  - Purpura
  - Renal failure
  - Neuropathy
- Severe hypertension/preeclampsia
  - Not autoimmune
  - Damage to vessel wall → fibrin leak

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# Inflammation Principles

## Inflammation Principles

Jason Ryan, MD, MPH

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## Inflammation

- Process for eliminating:
  - Pathogens
  - Damaged tissue
- Commonly seen with infections, trauma, surgery
- May cause damage to host:
  - Excessive inflammation (sepsis)
  - Prolonged (infection fails to resolve)
  - Inappropriate (autoimmune disease)

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## Inflammation

- Acute inflammation
  - Rapid onset (minutes to hours)
  - Quick resolution (usually days)
- Chronic inflammation
  - May last weeks, months, or years

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## Cardinal Signs

- Described by the ancient Romans
- Rubor (redness) and calor (warmth)
  - Caused by vasodilation and increased blood flow
- Tumor (swelling)
  - Increased vascular permeability
  - Brings cells/proteins (complement) to site of inflammation
- Dolor (pain)
- Loss of function
  - Caused by other cardinal features

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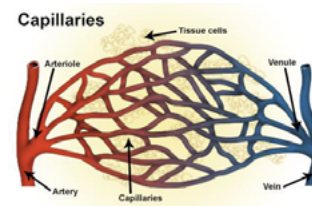
James Heilman, MD/Wikipedia

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## Vasodilation

Rubor and Calor

- Arteriolar vasodilation → increased blood flow



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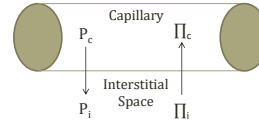
## Tissue Edema

- **Exudate**
  - Inflammatory edema from high vascular permeability
  - Seen in infection, malignancy (leaky vessels)
  - High protein content (similar to plasma)
  - High specific gravity (concentrated)

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## Tissue Edema

- **Transudate**
  - Cause: ↑ hydrostatic pressure or ↓ oncotic pressure
  - Fluid leak NOT due to inflammation
  - Low protein content (albumin remains in plasma)
  - Low specific gravity (dilute, not concentrated)



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## Pleural Effusion



James Heilman, MD

- Causes:
  - Exudate (infection, malignancy)
  - Transudate (heart failure, low albumin)
- Thoracentesis
- Fluid tested for protein, LDH
- Light's Criteria – Exudate if:
  - Pleural protein/serum protein greater than 0.5
  - Pleural LDH/serum LDH greater than 0.6
  - Pleural LDH greater than 2/3 upper limits normal LDH

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## Pain

Dolor

- Key mediator: PGE2
- Increases skin sensitivity to **pain**
- Also causes fever

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## Systemic Inflammation

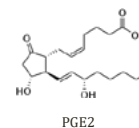
- Fever
- Leukocytosis
- Acute phase reactants



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## Fever

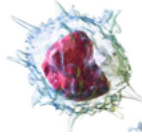
- Pyrogens
  - ↑ **cyclooxygenase** activity in hypothalamus
  - ↑ **prostaglandins** in hypothalamus
  - Lipopolysaccharide: exogenous pyrogen
  - IL-1 and TNF: endogenous pyrogens
- **Prostaglandins** alter temperature set point
  - Especially PGE2



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## Leukocytosis

- Normal WBC: <math>< 11,000/\text{mm}^3</math>
- Infection: 15,000-20,000/mm<sup>3</sup>
- Raging infection: 40,000-100,000/mm<sup>3</sup>
  - "Leukemoid reaction"
  - Resembles leukemia
- Cytokines (TNF and IL-1) → cells from bone marrow
- Bacterial infections: neutrophils (neutrophilia)
- Viral infections: lymphocytes (lymphocytosis)



BruceBlais/Wikipedia

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## Left Shift

- Normal response to infection
- More bands and neutrophils

	Normal	Infection
WBC	10,000/μL	17,000 /μL
Neutrophils	55%	80%
Bands	5%	12%

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## Acute Phase Reactants

- Serum **proteins**
- Levels rise with inflammation (acute or chronic)
- Mostly produced by **liver**
- Synthesis increased by **cytokines** often **IL-6**
- C-reactive protein
- Serum amyloid A
- Ferritin
- Hpcidin
- Fibrinogen



Pisabay/Public Domain

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## C Reactive Protein (CRP)

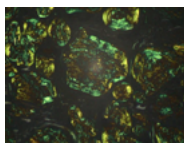
- Liver synthesis in response to **IL-6** (macrophages)
- Binds bacterial polysaccharides
- Activates **complement system**
- Chronic increased levels associated with CAD

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## Serum Amyloid A Proteins

SAA Proteins

- Apolipoproteins
- Many roles in inflammatory response
- Causes **AA (secondary) amyloidosis**
  - Occurs in chronic inflammatory conditions
  - Rheumatoid arthritis, ankylosing spondylitis, IBD



Ed Uthman, MD

Boards&Beyond

## Ferritin

- Binds iron
- Iron storage protein
- Stored intracellularly as ferritin
- Stored in **macrophages of liver and bone**
- Clinical significance:
  - Diagnosis of iron deficiency during infection

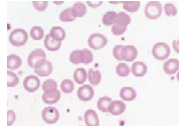


Tomihahndorf

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## Hepcidin

- Anti-bacterial properties
- Inhibits iron transport
  - Binds to **ferroportin** in enterocytes, macrophages
- **Iron trapped in cells as ferritin**
- Contributes to anemia of chronic disease



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## Fibrinogen

- Factor I of the clotting cascade
- Promotes **cellular adhesions**
- Platelets, endothelial cells

## ESR

Erythrocyte Sedimentation Rate

- Rate of RBC sedimentation in test tube
  - Normal 0-22 mm/hr for men; 0-29 mm/hr for women
- Increased by acute phase reactants in inflammation



MechESR/Wikipedia

## ESR

Erythrocyte Sedimentation Rate

- Determined by balance of factors
  - Pro-sedimentation: APRs, especially fibrinogen (sticky)
  - Anti-sedimentation: negative charge of RBC
- High levels APRs → red cells stick together
- Faster sedimentation → increased ESR

## ESR

Erythrocyte Sedimentation Rate

- ESR > 100 (normal <30) seen in:
  - Endocarditis
  - Temporal arteritis
  - Polymyalgia rheumatica
  - Trauma/surgery
  - Malignancy
- Anemia: Increased ESR
  - Sedimentation of red cells slower with more red cells
  - Red cells impeded one another's sedimentation
- Renal disease (some due to anemia)

## ESR

Erythrocyte Sedimentation Rate

- Reduced ESR (<5)
  - Hypofibrinogenemia
  - Heart failure (controversial; mechanism unclear)
- Abnormal red cell shapes
  - Sickle cell anemia
  - Spherocytosis
  - Microcytosis
- Polycythemia (opposite of anemia)
- Result: ESR may be normal despite inflammation

## Negative APRs

- Levels fall in inflammation
- Synthesis inhibited by cytokines
- **Albumin**
- Transferrin
- Transthyretin

# Acute and Chronic Inflammation

## Acute & Chronic Inflammation

Jason Ryan, MD, MPH

Boards&Beyond

## Inflammation

- Acute inflammation
  - Rapid onset (minutes to hours)
  - Quick resolution (usually days)
- Chronic inflammation
  - May last weeks, months, or years

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## Acute Inflammation

- Part of **innate immunity**
- Three hallmark features
  - Increased blood flow (vessel dilation)
  - Increased vascular permeability
  - Emigration of neutrophils into tissues
- Rapid onset/short duration
  - Occurs within minutes of trigger
  - Resolves in minutes/hours/days

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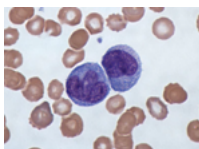
## Innate Immune System

- Phagocytes (debris clearing)
  - **Macrophages**
  - **Neutrophils**
- Complement
- Natural Killer Cells
- Eosinophils
- Mast cells and Basophils

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## Macrophages

- Macrophages: guardians of innate immunity
- Found in tissues; capable of phagocytosis
- Recognize cellular damage, microbes, foreign bodies
- Initiate acute inflammatory response
- Similar role played by mast cells, dendritic cells



Dr Graham Beards/Wikipedia

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## Macrophages

- Recognize molecules that are “foreign”
- “Damage-associated molecular patterns” (DAMPs)
  - Present only when tissue damage occurs
  - Example: mitochondrial proteins, DNA
- “Pathogen-associated molecular patterns” (PAMPs)
  - Present on many microbes
  - Not present on human cells

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## Macrophages

- Key receptors: **"Toll-like receptors"** (TLRs)
  - Macrophages, dendritic cells, others
  - Found on cell membrane and endosomes
  - Pattern recognition receptors
  - Recognize PAMPs/DAMPs → secrete cytokines
  - Activation → cytokines, inflammatory signals
- Other activators:
  - Fc portion of antibodies
  - Complement proteins

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## Inflammasome

- **Cytosolic protein complex** found in many cells
- Key for recognition of cell damage
- Activated by components of **damaged cells**:
  - Uric acid
  - Extracellular ATP
  - Free DNA
- Leads to production of **IL-1**
- Leads to release of inflammatory mediators

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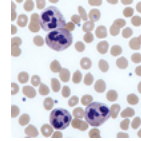
## Inflammatory Mediators

- "Vasoactive amines"
  - Histamine
  - Serotonin
- Lipid products (arachidonic acid derived)
  - Prostaglandins
  - Leukotrienes
- Complement

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## Neutrophil

- Derived from bone marrow
- Circulate ~5 days and die unless activated
- Drawn from blood stream to sites of inflammation
- Enter tissues: phagocytosis
- Provide extra support to macrophages



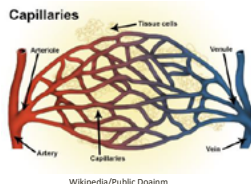
Dr Graham Beards/Wikipedia

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## Neutrophil

Blood stream exit

- Exit vascular system at post-capillary venules
- Four steps to extravasation (exit vessels to tissues)
  - Rolling, crawling, transmigration, migration



Wikipedia/Public Domain

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## Acute Inflammation

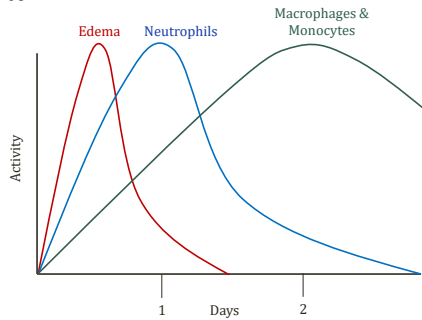
Typical Timeline

- Neutrophils dominate early (<2 days)
  - Many in blood stream
  - Attach firmly to adhesion molecules
  - Apoptosis after 24-48hrs
- Monocytes/macrophages dominate late (>2 days)
  - Live longer
  - Replicate in tissues

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## Acute Inflammation

Typical Timeline



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## Acute Inflammation

Typical Timeline: Exceptions

- **Pseudomonas infection**
  - Neutrophils dominate for days
- **Viral infections**
  - Lymphocytes often appear first
- **Hypersensitivity reactions**
  - Eosinophils dominate

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## Acute Inflammation

Resolution

- Three potential outcomes
- **#1: Resolution of inflammation**
  - Removal of microbes/debris
  - Tissue returns to normal
- **#2: Healing/scar**
  - Tissue damage too extensive for regeneration
  - Connective tissue growth
- **#3: Chronic inflammation**

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## Chronic Inflammation

- Prolonged inflammation (weeks/months)
- May follow acute inflammation
- May begin slowly (“smoldering”) on its own
- Tissue destruction and repair occur **at same time**

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## Chronic Inflammation

Causes

- **Persistent infections**
  - Difficult to clear microbes
  - Mycobacteria
  - Parasites
  - Prolonged infection → type IV hypersensitivity reaction
- **Autoimmune diseases**
- **Prolonged exposure**
  - Silica
  - Cholesterol (atherosclerosis)

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## Chronic Inflammation

Cells

- **Mononuclear cells**
  - Macrophages
  - Lymphocytes (T and B cells)
  - Plasma cells
- **Macrophages** are dominant cell type
  - Secrete cytokines
  - Activate T-cell response
- **Two forms activated macrophages**
  - M1: Activated via classical pathway to destroy microbes
  - M2: Activated via alternative pathway for tissue repair

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# Chronic Inflammation

## Macrophage Activation

- "Classical" activation (M1)
- Microbes activate macrophages
  - Example: endotoxin → TLRs on macrophages
- T-cell release **IFN-γ**
- Activated macrophage response
  - Reactive oxygen species
  - More lysosomal enzymes
  - Secrete cytokines → drive inflammation
- Tissue destruction may occur

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**IFN-γ**

# Chronic Inflammation

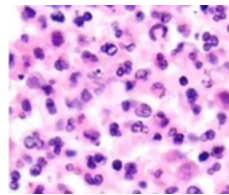
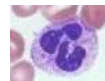
## Macrophage Activation

- "Alternative" activation (M2)
- Cytokines **other than IFN-γ**
  - Produced by T cells
  - IL-4, IL-13
- Activated macrophage (M2) response
  - Inhibit classical activation
  - Main role is **tissue repair**
  - Growth factors → angiogenesis

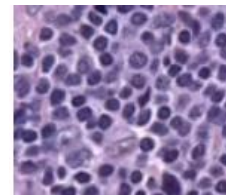
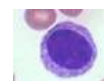
# Chronic Inflammation

## Outcomes

- Scarring
  - Chronic HBV → liver cirrhosis
- Secondary amyloidosis
- Malignancy
  - Lots of cell stimulation/growth
  - Similar to hyperplasia → dysplasia/neoplasia
  - Chronic hepatitis → liver cancer
  - H. pylori → gastric cancer



Acute Inflammation  
Neutrophils  
Multi-lobed nuclei



Chronic Inflammation  
Mononuclear cells  
Single, round nuclei

# Granulomatous Inflammation

## Granulomatous Inflammation

Jason Ryan, MD, MPH

Boards&Beyond

## Inflammation

- Acute inflammation
  - Rapid onset (minutes to hours)
  - Quick resolution (usually days)
- Chronic inflammation
  - May last weeks, months, or years

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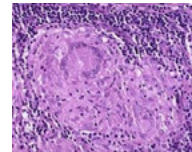
## Granulomatous Inflammation

- Subtype of **chronic** inflammation
- **Macrophages** transform to :
  - Epithelioid cells
  - Langhans giant cells
- **T-cell mediated** hypersensitivity reaction
  - Type IV (delayed-type) hypersensitivity reaction
  - Cell mediated immune process

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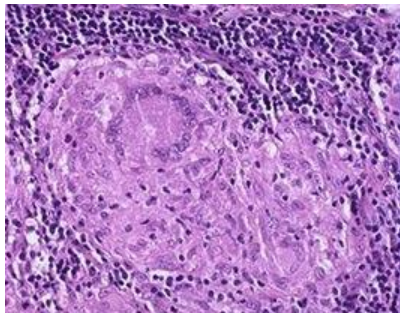
## Granulomas

- “Epithelioid” macrophages
  - Large, pink, activated macrophages (look like epithelial cells)
- Surrounded by lymphocytes (sometimes plasma cells)
- Some epithelioid macrophages fuse → giant cells
  - May contain 20 or more nuclei



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## Granulomatous Inflammation

- Accumulation of **TH1 CD4+ T cells**
  - High CD4:CD8 ratio
- Secrete IL-2 and interferon- $\gamma$ 
  - IL-2 stimulates T-cell proliferation
  - IFN- $\gamma$  activates macrophages
- Ultimately leads to granuloma formation

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granuloma  
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## Granulomatous Disease

- Tuberculosis
- Sarcoidosis (granulomas = diagnostic criteria)
- Crohn's disease
- Leprosy (mycobacterium leprae)
- Cat-scratch disease (bartonella henselae)
- Schistosomiasis
- Syphilis
- Temporal arteritis
- Many others

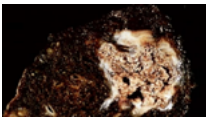
## CGD

Chronic Granulomatous Disease

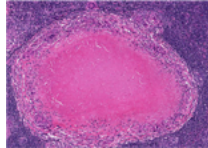
- Loss of function of NADPH oxidase
- Phagocytes cannot generate  $H_2O_2$
- **Recurrent catalase (+) bacteria infections**
- Five organisms cause almost all CGD infections:
  - Bacteria: Staph aureus, Pseudomonas, Serratia, Nocardia
  - Fungi: Aspergillus
- Granuloma formation

## Caseating Granuloma

- Gross pathology : cheesy-like (caseating) necrosis
- Microscopy: Granulomas with necrotic core
- Classically seen in **tuberculosis infection**
- Most granulomas: non-caseating (e.g., sarcoid)



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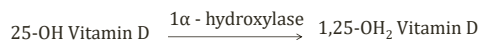
## Tumor Necrosis Factor Alpha

TNF- $\alpha$

- Maintains granulomatous inflammation
- Released by macrophages and T-cells
- Attracts and stimulates macrophages
- **TNF-blocking drugs**
  - Used in rheumatoid arthritis, Crohn's disease
  - Infliximab: anti-TNF antibody
  - Etanercept: decoy receptor TNF- $\alpha$
- PPD testing done prior to starting therapy

## Hypercalcemia

- Seen in many granulomatous diseases
- Best described in **sarcoidosis**
- Activated vitamin D produced only in kidney
  - Responds to PTH
- Macrophages: high 1- $\alpha$  hydroxylase activity
- Leads to increased vitamin D levels (calcitriol)



# Pathologic Calcification

## Pathologic Calcification

Jason Ryan, MD, MPH

Boards&Beyond

## Pathologic Calcification

- Abnormal deposition of calcium in tissues
- Dystrophic calcification
  - Local process
- Metastatic calcification
  - Systemic process

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## Dystrophic Calcification

- Result of **necrosis**
- Occurs in diseased tissues
- Examples:
  - Atherosclerotic vessel lesions
  - Damaged heart valves
  - Lung nodules
- May indicate prior necrosis
- May also cause disease
  - Aortic stenosis

Carotid Artery

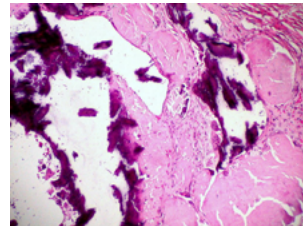


Ed Uthman

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## Dystrophic Calcification

- Purple deposits on H&E staining

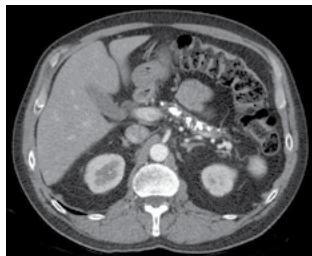


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## Chronic Pancreatitis

- CT scan: classic finding is **calcified** pancreas

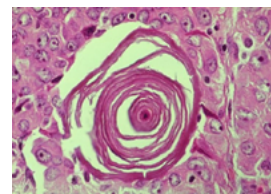


Hellerhoff/Wikipedia

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## Psammoma Bodies

- Calcifications with an layered pattern
- Seen in some neoplasms (e.g., thyroid cancer)



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## Dystrophic Calcification



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## Dystrophic Calcification

- Serum calcium levels **normal**
- Damage to **phospholipid membranes** in cells
- Calcium binds phospholipids
- Enzymes add phosphate
  - Similar to calcium-phosphate of hydroxyapatite in bone
- Generates microcrystals
- Crystals propagate → calcification

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## Metastatic Calcification

- Seen in **hypercalcemia** and/or **hyperphosphatemia**
- Occurs in normal tissues
- Mostly tissues that secrete acid
  - Create high pH internally
  - Favors calcium phosphate precipitation

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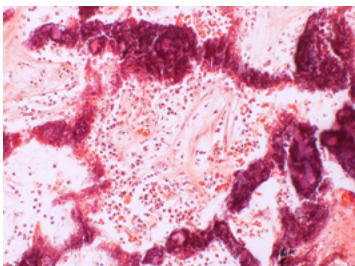
## Metastatic Calcification

- Classic locations:
  - GI mucosa
  - Kidneys
  - Lungs
  - Arteries
  - Pulmonary veins

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## Metastatic Calcification

Alveolar Walls



Yale Rosen/Flickr

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## Calciphylaxis

- Seen in chronic **hyperphosphatemia in CKD**
- Excess phosphate taken up by vascular smooth muscle
- Smooth muscle osteogenesis
- Vascular wall calcification
- Increased systolic blood pressure
- Small vessel thrombosis
- Painful nodules, skin necrosis



Niels Olsen/Wikipedia

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## Nephrocalcinosis

- Calcium deposition in **kidney tubules**
- Cause: ↑ urinary excretion of calcium and phosphate
- Seen in hypercalcemia and hyperphosphatemia
  - e.g., hyperparathyroidism, sarcoidosis
- Common in patients with kidney stones

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## Nephrocalcinosis

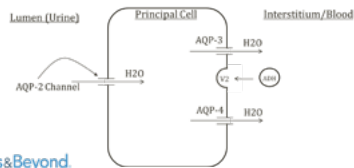


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## Nephrocalcinosis

- Often asymptomatic
- May cause **polyuria/polydipsia**
  - Nephrogenic diabetes insipidus
  - Impaired urinary **concentrating** ability
  - Collecting duct cannot resorb water normally
  - More urine → polyuria → volume depletion → polydipsia



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# Wound Healing and Scar

## Wound Healing and Scar

Jason Ryan, MD, MPH

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## Wound Healing

- Necessary after inflammation/cell death
- **Regeneration**
  - Occurs in tissues capable of replacing damaged cells
  - Must have surviving cells capable of division
- **Scar formation**
  - Tissues not capable of regeneration
  - Or if severe damage that destroys regenerative capacity
  - Lost cells replaced by connective tissue
  - "Fibrosis": scar tissue left at sites of inflammation

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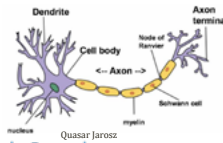
## Tissue Types

- **Labile tissues**
  - Continuously dividing to replace lost cells
  - Hematopoietic stem cells
  - Most epithelial cells
  - Easily regenerate
- **Stable tissues**
  - Inactive ("quiescent") cells
  - Normally replicate minimally
  - Can proliferate in response to injury
  - Many solid organs: liver, kidney, pancreas

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## Tissue Types

- **Permanent tissues**
  - "Terminally differentiated"
  - Generally do not proliferate (very limited ability)
  - Cannot significantly regenerate
  - Neurons, cardiac myocytes
  - Damage leads to scar



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## Stem Cells

- Mature cells of many tissues have short lifespan
- Stem cells replace lost cells
- **Self-renewal** and **asymmetric division**
  - Two daughter cells
  - One becomes mature cell
  - Other becomes stem cell

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## Stem Cells

- **Embryonic** stem cells
  - Found in blastocyst
  - Undifferentiated
  - Can form many different cells types
  - Important for embryogenesis
- **Adult** stem cells
  - Found in tissue beds
  - More differentiated
  - Produce cells for one tissue (e.g., skin, epithelial lining)
  - Important for homeostasis (replacing lost cells)

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## Scar Formation

- Sequence of three processes
- #1: Angiogenesis (new blood vessel growth)
- #2: Fibroblast activation
  - Migrate to injury site
  - Proliferate
  - Lay down fibrous tissue
- #3: Scar maturation
  - Changes to scar composition/structure
  - Produces stable, stronger scar tissue

## Growth Factors

- Drive scar formation
- Many, many factors described
  - FGF
  - TGF- $\beta$
  - VEGF
  - PDGF
  - Metalloproteinases
  - EGF
- Most trigger chemotaxis, angiogenesis, fibrosis

## Angiogenesis

- First process in healing/scar formation
- New vessel growth from existing vessels
- Usually new vessels grow from **venules**
- Key growth factors:
  - VEGF
  - FGF

## VEGF

Vascular endothelial growth factor

- Family of signal proteins
- Several forms (VEGF-A/B/C/D)
- VEGF-A: Stimulates **angiogenesis**
- Secreted by tumors  $\rightarrow$  vascular growth
- VEGF Inhibitors
  - Bevacizumab (cancer)
  - Ranibizumab (retinopathy)

## FGFs

Fibroblast Growth Factors

- Sources: macrophages, mast cells, endothelial cells
- Attract fibroblasts ("chemotactic")
- Stimulates **angiogenesis**
- Also stimulates extracellular matrix protein synthesis

## Fibroblasts

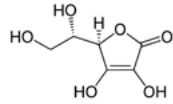
- Fibroblasts migrate to injury site
- Extracellular matrix proteins synthesized/secreted
- Initially **secrete type III collagen** and **fibronectin**
- Later collagen type III broken down
- Followed by secretion of type I collagen occurs
- Key growth factors:
  - TGF- $\beta$
  - PDGF



## Vitamin C

Ascorbic Acid

- Found in fruits and vegetables
- Necessary for **collagen synthesis**
- Poor wound healing in deficiency state



Jina Lee/Wikipedia

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## TGF- $\beta$

Transforming Growth Factor Beta

- Released by many cell types:
  - Platelets, T cells, macrophages, endothelial cells, others
- Promotes healing/scar
  - Stimulates **collagen production**
  - Inhibits collagen breakdown
- Anti-inflammatory
  - Inhibits lymphocyte proliferation/activity
  - Knock-out mice (no TGF- $\beta$ ): widespread inflammation

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## PDGF

Platelet-derived growth factor

- Sources: platelets, macrophages, endothelial cells
- Stimulates **fibroblasts** and smooth muscle cells
  - Growth, migration of fibroblasts
  - Synthesis of collagen
- Implicated in myelofibrosis, scleroderma

P  
D  
G  
F  
Fibroblast

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## Granulation Tissue

- Develops 3 to 5 days after injury
- Early stages healing/scar formation
- Made of collagen and new blood vessels
- Histology:
  - Proliferating fibroblasts
  - Small, new capillaries from angiogenesis
  - Extracellular matrix
  - Some inflammatory cells especially macrophages
- Eventually becomes scar

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## Granulation Tissue



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## Myofibroblasts

- Fibroblasts with **contractile proteins**
- Share similarities with smooth muscle cells
- **Contract wound** (pull edges together)
  - Wound size shrinks
- Develops around day 5 after injury
- Lost by apoptosis as scar matures

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## Remodeling

- Modification of connective tissue
- Occurs after initial synthesis/deposition
- Key features:
  - Breakdown of type III collagens
  - Cross-linking of collagen
- Key enzymes:
  - Metalloproteinase (zinc)
  - Lysyl oxidase (copper)

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## Metalloproteinases

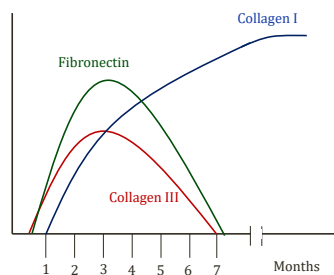
- Zinc containing enzymes
- Degrade proteins in extracellular matrix
- Important for maturation phase of wound healing
- Breakdown type III collagen
  - “Collagenase” activity
- **Zinc deficiency:** poor wound healing (maturation)



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## Wound Healing



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## Lysyl Oxidase

- Copper-dependent enzyme
- Cross-links collagen
- **Cu deficiency:** poor wound healing (maturation)



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Surgical Wound



Carsten Niehaus/Wikipedia

Pressure Ulcer



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## Skin Wound Healing

- First intention
  - Tissue surfaces “approximated” (i.e., closed together)
  - Common method of healing for surgical incision sites
  - Sutures, staples, skin glue, tape
  - Requires relatively small amounts of tissue loss
  - Main mechanism of healing: **epithelial regeneration**
  - Minimal scar
  - Minimal wound contraction

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## Skin Wound Healing

- Second intention
  - Large wounds
  - Cannot approximate edges
  - Classic example: pressure ulcer
  - Significant scar formation

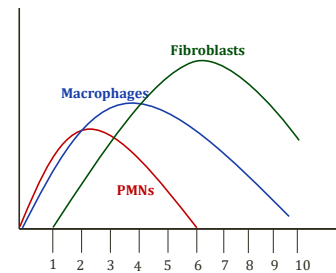
## Healing by 1<sup>st</sup> Intention

- Injury site:
  - Tissue loss
  - Blood loss (damaged vessels)
- 1<sup>st</sup> 24 hours
  - Inflammation and hemostasis
  - **Clot formation** (platelets)
  - Neutrophil invasion (via increased vascular permeability)

## Healing by 1<sup>st</sup> Intention

- 3-7 days
  - Neutrophils replaced by macrophages
  - **Angiogenesis**
  - **Fibroblast** infiltration
  - Granulation tissue formation
  - Type III collagen
  - Wound contraction via myofibroblasts
- Weeks
  - Remodeling
  - Type III collagen → **type I collagen**
  - Lysyl oxidase

## Cells in Healing



## Healing by 2<sup>nd</sup> Intention

- More inflammation
- More granulation tissue
- More tissue contraction
- More scar tissue

## Long Term Outcomes

- Scar remodeling may continue for **6-12 months**
- Eventually a “mature” scar forms
  - Avascular
  - Acellular
- **Mechanical strength grows**
  - Type 1 collagen content grows
  - Collagen synthesis stops after a few weeks
  - Collagen cross-linking persists long after
- Scar gets stronger over time
- Tensile strength never equal that of normal tissue

## Keloid

- Raised scars
- Extend beyond borders of original wound
- Caused by excessive healing/scar
  - More fibroblasts, more growth factors, more collagen



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## Keloid

- Contain type I and III collagen
- Disorganized collagen
  - Contrast with normal skin: collagen parallel to epithelium
- More common in certain locations
  - Common in earlobe, deltoid, upper back
  - Rare on eyelids, palms, soles
- High recurrence rate if surgically removed
- Treatment: corticosteroid, 5-FU injections

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## Hypertrophic Scars

- Also excessive scar formation
- Usually develop about 4 weeks after injury
- **Remains within wound borders**
- Mostly **type III collagen**
  - Parallel (not disorganized) fibers
- May occur anywhere
- Often regress spontaneously

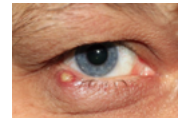


Cgomez447 /Wikipedia

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## Wound Infections

- Disrupt healing process
- Prolonged inflammation phase
- **Pus** = bacteria plus dead neutrophils
- Inflammatory cytokine release continues
- Poor formation of growth factors



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## Wound Infections

- Staph Aureus
- Clostridium tetani (vaccination after injury)
- Pseudomonas (burns)
- Rabies virus (vaccination after animal bites)
- Vibrio vulnificus (contaminated water)



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# Neoplasia

## Neoplasia

Jason Ryan, MD, MPH

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## Neoplasia



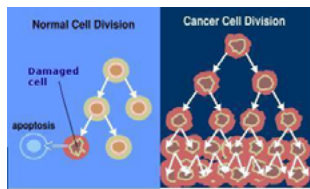
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- "New growth"
- Cancer, malignancy
- **Genetic disorder**
- Cell cycle normally tightly controlled
  - Signals → growth/cell divisions
  - Signals → prevention of growth/cell division
- Mutations → uncontrolled growth

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## Clonality

- Single cell develops mutation
- Gives rise to daughter cells (clones)
- All clones carry same mutation



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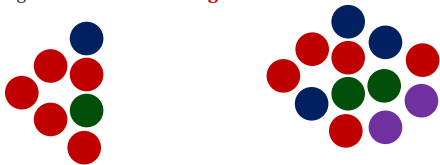
## Tumor Locations

- Rapidly dividing cells
  - Stop/start for cell division
  - Lots of DNA replication
  - Many chances for mutation
  - Increased likelihood of cancer
- GI epithelium: common site of cancer
- Myocardium: very rare site of cancer

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## Tumor Progression

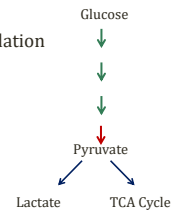
- Change in tumor over time
- Become more aggressive
- Accumulate more mutations
- Less responsive to chemotherapy
- Large tumors often **heterogenous**



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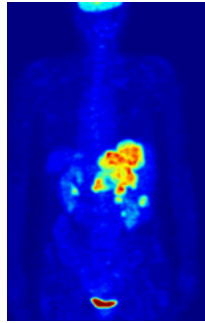
## Warburg Effect

- Glucose metabolized to lactate for ATP
  - "Aerobic glycolysis"
- Less ATP than oxidative phosphorylation
- Occurs even in presence of oxygen
- Result: **High glucose uptake**
- Basis for PET scanning
  - Radiolabeled glucose scan



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## PET Scan



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## Dysplasia

- Description of tissue morphology
- Disordered but non-neoplastic growth
- Precedes neoplasia
- Progresses to cancer
- Described in epithelial tissues
- Carcinoma in situ
  - Dysplasia of entire epithelial layer
  - No invasion of basement membrane (contained)

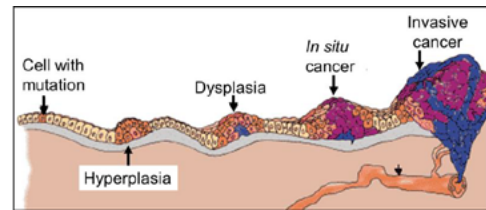
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## Anaplasia

- **Undifferentiated** cell growth
- Cells do not look like cells of origin
- Metabolic activity to growth
- Little/no other functions
- Seen in malignant, aggressive tumors
- Usually poor prognosis
- Well-differentiated tumors: resemble tissue or origin
- Anaplastic tumors: lack of distinguishing features

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## Cancer Progression



Danielah67/Wikipedia

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## Hallmarks of Malignant Cells

- **Autonomous growth**
  - Not sensitive to growth factors/inhibitors
- Evasion of cell death
  - Do not undergo apoptosis
  - Evade the immune system
- Unlimited ability to replicate ("**immortal**")
  - Normal cells become "senescent" after XX replications
- Angiogenesis
  - New blood vessels to fuel growth
- Ability to invade tissues and spread

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## Telomerase

- Normal cells capable of 60-70 divisions only
  - Thereafter become senescent
- Caused by shortening of **telomeres**
- Telomeres: nucleotides at end of chromosomes
- Telomerase: avoids loss of genes with duplication
  - Active in stem cells
  - Little activity in other cells
- **Telomerase upregulation** in almost all cancers



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## Grade

- Degree of differentiation
- Determined by pathologist
- Requires **biopsy** for microscopic tissue analysis
- Grades I, II, III, IV
- Well-differentiated: low grade
- Anaplastic/undifferentiated: high grade

## Stage

- Degree of tumor extension/spread
- Local, lymph nodes, metastasis
- Usually done by **radiology/imaging**
- Early stage: localized growth
- Advanced stage: spread, metastasis

## TNM Staging System

- T: primary tumor size
  - T1, T2, T3, T4
- N: degree of regional lymph node spread
  - N0, N1, N2, N3
- M: metastases
  - M0=no mets; M1 = mets

# TNM

## Nomenclature

- **Benign**
  - Likely to remain localized without spread
  - Amenable to surgical removal
  - May still cause problems (e.g., compression)
  - Well-differentiated
  - Low mitotic activity
- **Malignant**
  - Invades and spreads
  - May cause death

## Non-neoplastic Growths

- **Hamartoma**
  - Mass of mature but disorganized cells
  - Example: lung hamartoma contains disorganized lung tissue
  - Developmental anomalies
- **Choristoma**
  - Mature, well-differentiated tissue in the wrong place
  - Example: Meckel's diverticulum (gastric tissue in ileum)
- Both are benign (i.e., do not invade/metastasize)

## Tumor Naming

### Benign Tumors

- Naming: cell/tissue type of origin plus -oma
  - Fibroma: benign fibrous tumor
  - Chondroma: benign cartilage tumor
- Adenoma
  - Benign epithelial tumors
  - Often forming gland structures
- Papilloma
  - Benign epithelial tumors on surfaces with "finger-like" projections

## Tumor Naming

### Malignant Tumors

- Mesenchymal tissues
  - Connective tissue, bones, blood, lymph
  - Solid tumor: sarcoma (e.g., osteosarcoma)
  - Blood/lymph: leukemia or lymphoma
- Epithelial cells: carcinoma
  - Glandular tumors: adenocarcinoma
  - Colon adenocarcinoma, lung adenocarcinoma
  - Skin: squamous cell carcinoma

## Tumor Spread

- Sarcoma: spread via blood (hematogenous)
  - Arteries (thick walls) difficult to penetrate
  - Veins (thin walls): easily penetrated
  - Liver and lungs most common sites of hematogenous spread

## Tumor Spread

- Carcinoma: usually spread via lymphatics
- Key exceptions:
  - **Four carcinomas** spread via bloodstream
  - Choriocarcinoma ("Early hematogenous spread")
  - Renal cell carcinoma (renal vein)
  - Hepatocellular carcinoma (portal vein)
  - Follicular thyroid carcinoma

## Teratoma

- Cells from multiple germ layers
  - Ectoderm (skin, hair follicles)
  - Endoderm (lung, GI)
  - Mesoderm (muscle, cartilage)
- Arise from **germ cells** in ovaries and testes
  - Cells of origin capable of forming multiple germ layers

## Epidemiology

- Cancer is 2<sup>nd</sup> leading cause of death
  - Heart disease #1
  - Respiratory disease #3 (e.g., COPD)
  - Accidents/trauma #4
- New cases (incidence)
  - Breast/prostate → lung → colorectal
- Mortality (death rate)
  - Lung → breast/prostate → colorectal

## Epidemiology

### Children

- Causes of death
  - Accidents → cancer → congenital disorders
- Incidence/mortality
  - Leukemia → CNS tumors → neuroblastoma



## Carcinogenesis

- Nonlethal DNA damage → cancer
- Mutations in two types of genes lead to cancer
  - Tumor suppressor genes
  - Oncogenes

## Tumor Suppressor Genes

- Limit cell growth
- Classic examples:
  - P53 gene: blocks progression through cell cycle
  - Retinoblastoma gene: inhibits transcription factors
- Need mutations in **both alleles** to shut down activity

## Germline Mutations

- One gene mutated in **all cells** at birth
- Occurs in some tumor suppressor genes
- Leads to increased cancer risk at early age
  - BRCA1/BRCA2 (breast cancer)
  - Hereditary retinoblastoma
  - HNPCC (Lynch syndrome)
  - Familial Adenomatous Polyposis (FAP)
  - Li-Fraumeni syndrome

## Oncogenes

- Promote uncontrolled cell growth
- Proto-oncogenes: normal cellular genes
  - Growth factors, growth factor receptors, signal transducers
  - Proto-oncogene mutation → oncogene → cancer
- **Single gene mutation** → malignancy

## Carcinogens

- Substances that cause cancer
- Chemicals
  - Asbestos → mesothelioma
- Viruses
  - HPV → cervical cancer
- Radiation
  - Sunlight → skin cancer