

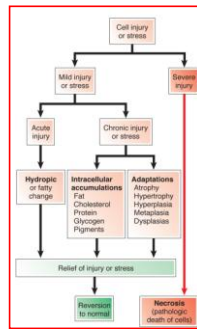
The Nature of Disease
Pathology for the Health Professions

Thomas H. McConnell

Chapter 2
Cellular Pathology:
Injury, Inflammation, and Repair

Overview of Cellular Injury

- Cells can be injured in several ways.
 - Anoxia, hypoxia, ischemia
 - Physical, chemical, radiation, toxins, microbes, inflammation and immune reactions, nutrition, genetic/metabolic, aging
- Mild injury or stress causes reversible cell change.
 - Atrophy, hypertrophy, hyperplasia, metaplasia, dysplasia
- Severe injury or stress causes cell death.
 - Apoptosis, necrosis



McConnell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014

Hypoxic Injury

- **Lack of sufficient O₂ (hypoxia) is the most common cause of cellular injury.**
- Causes of hypoxic injury
 - Reduced amount of atmospheric O₂
 - Decreased amount or function of Hb
 - Respiratory/Cardiovascular diseases
 - Poisoning of oxidative enzymes (cytochromes)
- **Ischemia (reduced blood supply) most common; nutrient delivery also compromised**
- **Anoxia (total lack of O₂)**

Major Cellular Responses to Hypoxia

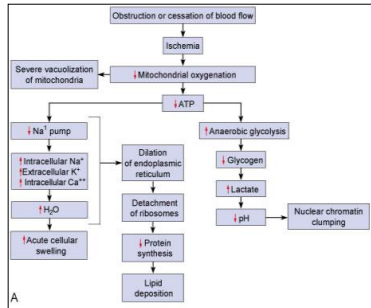


Figure from: Huether & McCance, *Understanding Pathology*, 5th ed., Elsevier, 2012

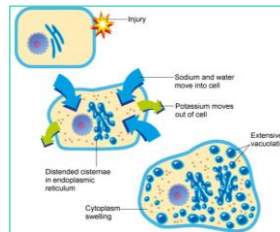
Fig. 3-7 Hypoxic injury induced by ischemia. A. Consequences of decreased oxygen delivery or ischemia with decreased ATP. The structural and physiologic changes are reversible if oxygen is delivered quickly. Significant decreases in ATP result in cell death, mostly by necrosis. B. Mitochondrial damage can result in changes in membrane permeability, loss of membrane potential, and decreased ATP. Between the outer and inner membranes of the mitochondria are proteins that can activate the cell's suicide pathway, called apoptosis. C. Calcium ions are critical mediators of cell injury. Calcium ions are usually maintained at low concentrations in the cell's cytoplasm. Both ischemia and certain toxins can initially cause an increase in the release of Ca²⁺ from intracellular stores and later an increased movement (influx) across the plasma membrane.

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Cellular Accumulations: Water

- Shift of Na⁺ and extracellular water into cell is most common degenerative cellular change
- May occur after hypoxia as ATPase pumps shut down
 - Na⁺ moves into cell; K⁺ moves out
 - Intracellular osmotic pressure increases
 - Water is pulled into cell by osmosis
- Reversible, sublethal
- Organs ↑ weight, become pale

Figure from: Huether & McCance, *Understanding Pathology*, 5th ed., Elsevier, 2012



Process called 'hydropic change' or 'vacuolar degeneration'

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Some Potentially Injurious Chemicals - CO

- Carbon Monoxide (CO)
 - Toxic asphyxiant (like HCN, H₂S) – directly interferes with cellular respiration
 - Odorless, colorless, undetectable
- Alcohol (Ethanol, Methanol)
 - More than 10 million chronic alcoholics in US (estimated)
 - Contributes to over 100,000 deaths annually (50% drunk driving)
- Acids (H₂SO₄, HCl, HNO₃)
- Alkalis (NaOH, KOH, NH₃)

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Quick Overview - Unintentional/Intentional Injuries

- **Asphyxial injuries**
 - Failure of cells to receive or use O₂
 - Suffocation – O₂ fails to reach the blood
 - Choking asphyxiation - obstruction of internal airways
 - Strangulation – compression/closure airways/bloodvessels
 - Chemical asphyxiants (CN⁻, H₂S)
- **Drowning**
 - May be wet (water in lungs) or dry (no water in lungs)
 - If survived, better if it occurs in cold water
- **Frostbite**
 - Freezes water inside cells
 - Ice crystals disrupt cell membranes
- Infectious, Immunologic, and Inflammatory (later)

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Ionizing Radiation

- Radiation strong enough to ionize H₂O
 - Splits H₂O into H⁺ and OH⁻
- **Acute**
 - OH⁻ attaches to DNA
 - Prevents cell replication
 - Most important in actively dividing tissues, e.g. GI tract, bone marrow
 - Decreased WBCs and GI epithelial loss -> predispose to infection
- **Chronic**
 - May cause DNA mutations
 - Development of neoplasia

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Cellular Adaptation to Chronic Injury/Stress

- **Atrophy** – decrease in cell size
- **Hypertrophy** – increase in cell size
- **Hyperplasia** – increase in cell number
 - Hormonal (estrogen-dependent organs)
 - Pathologic (abnormal; hormones/growth factors)
- **Metaplasia** – replacement of one mature cell type with a less mature cell type (reversible)
- **Dysplasia** (atypical dysplasia)
 - Not a true adaptive change
 - Deranged cellular growth
 - Abnormal size, shape, organization; precancerous

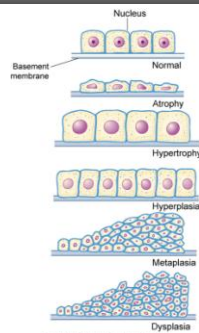
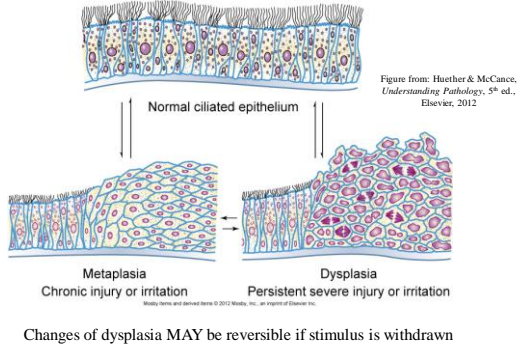


Figure from: Haether & McCance, *Understanding Pathology*, 5th ed., Elsevier, 2012

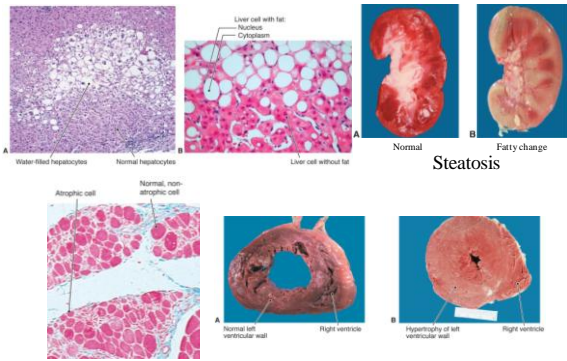
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Changes in Bronchi to Chronic Irritation



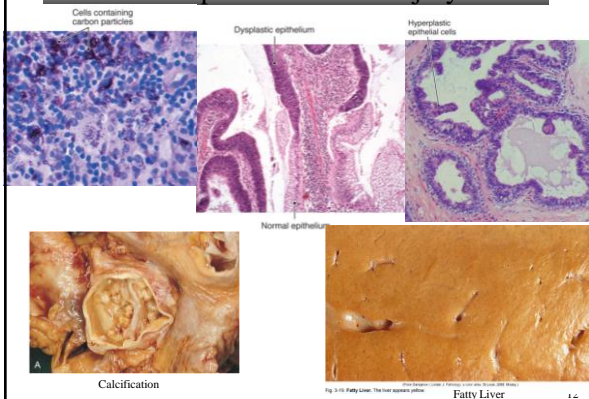
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Examples of Cellular Injury



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Examples of Cellular Injury



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Cell Death: Necrosis

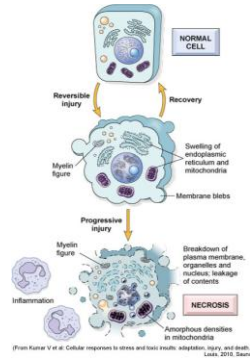
- **Necrosis**

- Cells die from some sudden insult

- **Undergo autolysis**

- Karyolysis (nuclear dissolution)
 - Pyknosis (nuclear shrinkage)
 - Karyorrhexis (nuclear fragmentation)
 - Disintegration of cellular organelles

- Leakage of cell contents causes inflammation in surrounding area



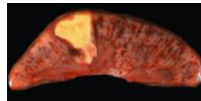
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Cell Death: Types of Necrosis

- **Four major types**

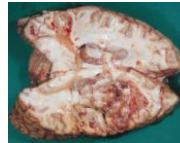
1. **Coagulative (kidney, heart, adrenals)**

- Typically from ischemia/hypoxia
 - Protein denaturation; albumin becomes gelatinous



2. **Liquefactive (nervous tissue)**

- Typically from ischemia/hypoxia
 - Cells digested by their own hydrolases
 - May be caused by bacteria infection



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Cell Death: Types of Necrosis

- **Four major types**

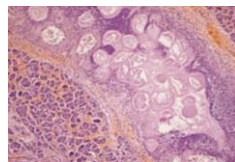
3. **Caseous (pulmonary tuberculosis)**

- Combination of coagulative and liquefactive
 - Tissue has 'clumped cheese' appearance



4. **Fat necrosis (breast, pancreas, abdominal organs)**

- Lipase breakdown of TG
 - FAs combine with Ca^{2+}
 - Saponification (soap is formed)

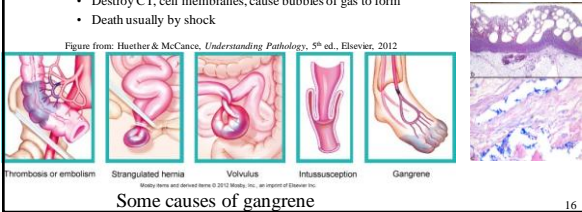


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Cell Death: Gangrenous Necrosis

- Occurs over a large area (rather than at the cellular level)
 - Typically from ischemia/hypoxia (particularly in lower limbs)
 - Dry: result of caseous necrosis
 - Wet: neutrophil invasion resulting in liquefactive necrosis
- Gas gangrene
 - Invasion of *Clostridium* sp. (anaerobes)
 - produce hydrolytic enzymes and toxins (exotoxins)
 - Destroy CT, cell membranes, cause bubbles of gas to form
 - Death usually by shock

Figure from: Huether & McCance, *Understanding Pathology*, 5th ed., Elsevier, 2012



Some causes of gangrene

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Cell Death: Apoptosis

- Active (not accidental) process
 - No accompanying inflammation
 - Part of normal physiology
 - Embryogenesis
 - Involvement of hormone-dependent tissue
 - Normal cell loss
 - Elimination of harmful (self-reactive) lymphocytes
 - May also occur in pathologic states
 - Severe cell injury
 - Accumulation of misfolded proteins
 - Infections
 - Obstruction of tissue ducts

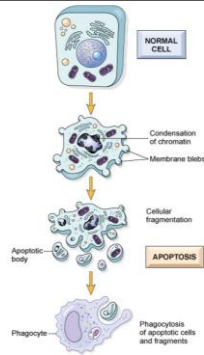


Figure from: Huether & McCance, *Understanding Pathology*, 5th ed., Elsevier, 2012

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Cell Death: Mechanisms of Apoptosis

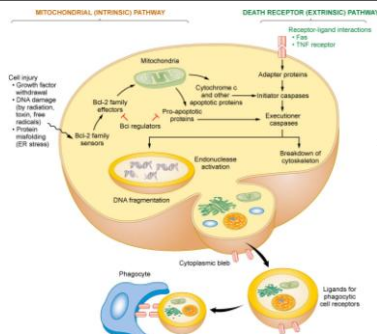


Figure from: Huether & McCance, *Understanding Pathology*, 5th ed., Elsevier, 2012

Fig. 3-30. Mechanisms of apoptosis. The two pathways of apoptosis differ in their induction and regulation, and both culminate in the activation of "executioner" caspases. The induction of apoptosis by the mitochondrial pathway involves the Bcl-2 family, which causes leakage of mitochondrial proteins. The regulation of the death receptor pathway involves the proteases, called caspases.

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The Inflammatory Response to Injury

- Leukocytes are the cells of inflammation
- Chemical signals mediate the inflammatory process
- The initial inflammatory response is vascular
- Cellular reaction follows vascular reaction
- Acute inflammation follows brief injury
- Chronic inflammation occurs with persistent injury.
- Inflammation has effects beyond the site of injury

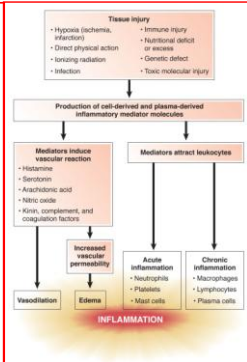
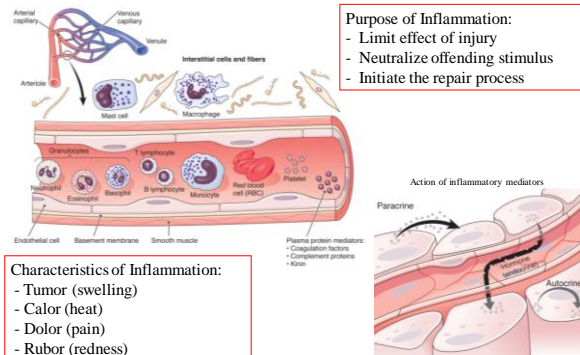


Figure from McConnell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014.

Components/Characteristics of Inflammation

- Purpose of Inflammation:
- Limit effect of injury
 - Neutralize offending stimulus
 - Initiate the repair process

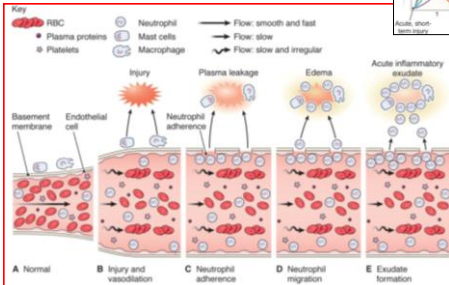
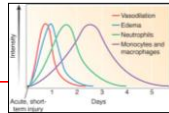


- Characteristics of Inflammation:
- Tumor (swelling)
 - Calor (heat)
 - Dolor (pain)
 - Rubor (redness)
 - Functio Laesa (loss of function)

Figures from McConnell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014.

Sequence of Events in Acute Inflammation

Acute Inflammatory Response: Note that vascular events (hyperemia, edema) come first, then cellular events



Figures from McConnell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014.

Acute Inflammatory Exudate

- Accumulation of fluid and WBCs at injury site
- Three major anatomic patterns:

– Serous inflammation

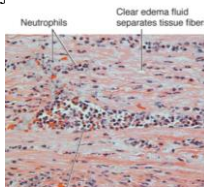
- Seen in mild, short-term inflammation
- Watery fluid with decreased protein
- No/few inflammatory cells

– Fibrinous inflammation

- Seen in more severe injuries
- Thicker, with coagulation factors (fibrin)
- Neutrophils

– Suppurative (purulent, pyogenic) inflammation

- Seen with severe injuries
- Associated with liquefactive necrosis; pus (dead cells/debris)
- Frequently associated with bacterial infection



Capillary packed with neutrophils
Figure from: McConaill, The Nature of Disease, 2nd ed., Wolters Kluwer, 2014

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Resolution of Acute Inflammation

- Most acute inflammation heals quickly unless an abscess is present or chronic inflammation develops
- **Complete resolution**
 - Mild Injury
 - Cells, debris, fluid cleared from site
- **Scarring** with severe or repeated acute inflammation
- **Chronic inflammation** may develop if cause of initial inflammation persists

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Chronic Inflammation

- Persistence of injurious agent is its hallmark
- Mixture of ongoing inflammation and healing
- Usual causes:
 - Persistent infection
 - Autoimmune disease
 - Persistent exposure to injurious agents
- Characteristics
 - Less intense than acute inflammation
 - Usually hot, swollen, red, and tender
 - Marked by lymphocytic infiltrate
 - May result in granulomatous inflammation

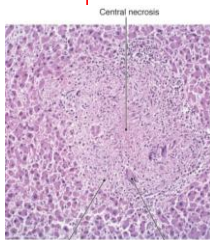


Figure from: McConaill, The Nature of Disease, 2nd ed., Wolters Kluwer, 2014

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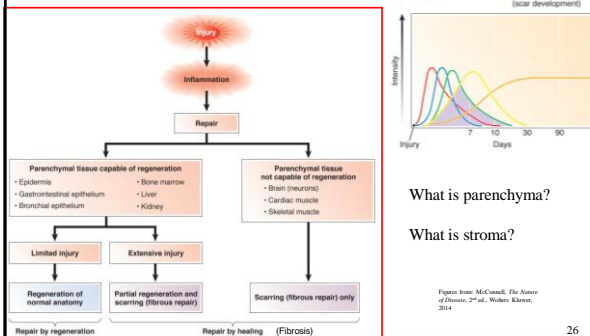
Non-local Effects of Inflammation

- Lymphatic System
 - Lymphangitis (inflammation of lymph vessels)
 - Lymphadenitis (infected lymph nodes)
 - Lymphadenopathy (lymph node enlargement)
 - Reactive hyperplasia (non-infected enlargement)
- Systemic Effects
 - Inflammatory mediators enter blood
 - In brain: fever, malaise, drowsiness, loss of appetite
 - In liver: production of reactant proteins
 - C-reactive protein – very reliable marker of inflammation
 - Fibrinogen – Increased ESR

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Tissue Repair - Overview

Wound – Acute (short-term) injury at discrete site



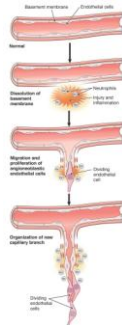
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Fibrous Repair Generates Scar Tissue

- Three step sequence in fibrous repair

Forms granulation tissue

- Cell migration and proliferation
 - Myofibroblasts proliferate begin producing collagen
 - Fills space not occupied by parenchymal cells
- Angiogenesis
 - Growth of new blood vessels
- Scar development
 - Myofibroblasts generate CT matrix
 - Pull edges of wound closed
 - Dense, tight, bloodless
 - Scar is remodeled by mechanical forces



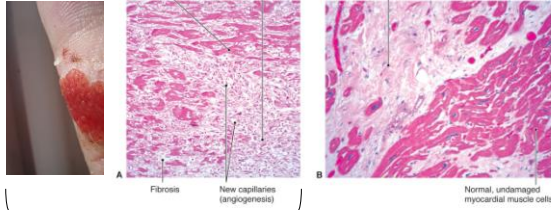
Figures from: McCosell, The Nature of Disease, 2nd ed., Wolters Kluwer, 2014

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Granulation Tissue and Scarring

Figures from: McCrannell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014

Figure from: https://en.wikipedia.org/wiki/Granulation_tissue



Granulation tissue

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Impaired Wound Healing

- Some factors interfering with wound healing include infection, poor nutrition, steroids, poor blood supply, foreign bodies and mechanical factors
- **Dehiscence** – rupture of a wound
- Two main types of pathological wound healing
 - Keloid; prominent, hyperplastic scar
 - Pyogenic granuloma; highly vascular, persistent granulation tissue

Figure from: McCrannell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014



Figure from: http://www.medic.net/en/image-collection/pyogenic-granuloma_skin_picture/picture.htm

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