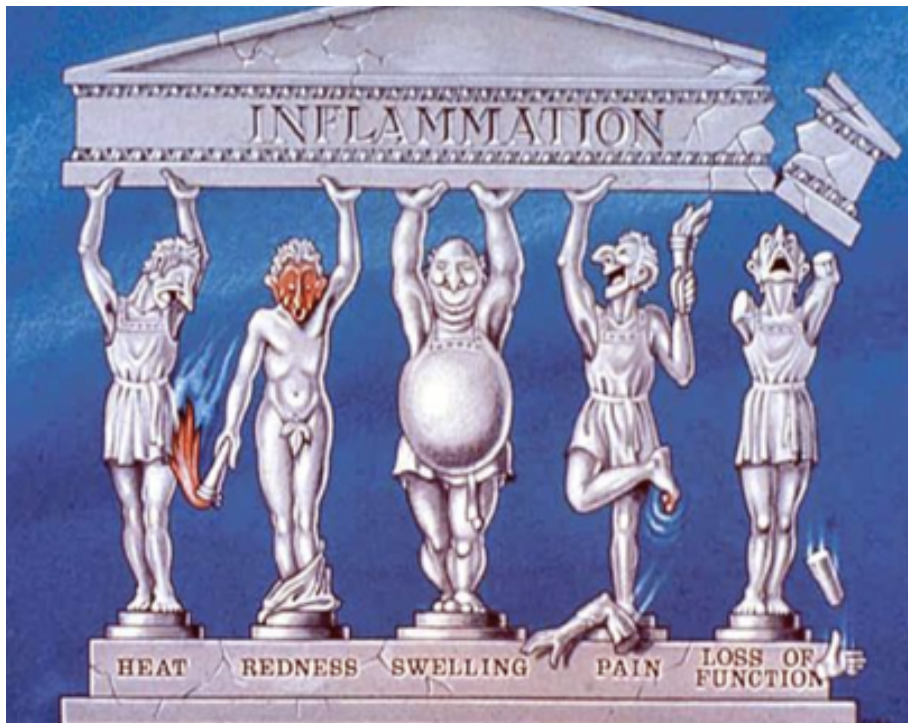


Inflammation

Dr. Gary Mumaugh – Campbellsville University



Inflammation

- The body's response to localized injury
- NOT simply "swelling"
- Many manifestations:
 - "Rubor" (redness)
 - "Calor" (heat)
 - "Tumor" (swelling)
 - "Dolor" (pain)
 - "Functio Laesa" (loss of function)
- Medical Terminology
 - Inflammation = **-itis**

Normal Vascularized Connective Tissue

- Inflammation focused in **loose connective tissue**
- Vessels participating in inflammatory response
 - Pre-capillary sphincters → capillaries
 - Regulates blood flow
 - Post-capillary venules
 - Epithelial junctions loosened allows more fluid to leave
 - Macrophages and Mast cells increase in inflamed tissues
- **Blood Hydrostatic Pressure (BHP)** - Physical pressure exerted by blood in vessels, forms tissue fluid
- **Tissue Osmotic Pressure (TOP)** - Solutes in interstitial spaces pull fluid out of capillaries
- **Blood Osmotic Pressure (BOP)** - Osmotic attraction of the blood for water
- **Tissue Hydrostatic Pressure (THP)** - work with BOP to force fluid back into vessels
- Excess fluid in tissue drained by lymph capillaries
 - Increased when tissue inflamed

Acute Inflammation Components

- **Vascular Component**
 - Increased blood flow and venule permeability to damaged tissue
 - Leads to rubor (redness), calor (heat), tumor (swelling)
- **Cellular Component**
 - Many leukocytes infiltrate damaged tissue
 - Inactivate disease-causing agents
 - Remove debris
 - **Exudate** - Collection of fluid, cells, and other materials moving into damaged tissues during an inflammatory response

Exudate Formation: Vascular Level

- **Exudate** - fluid and plasma accumulation
 - **Hyperemia** - vasodilation of arterioles = Increased blood flow in an area of the body
 - Chemicals cause:
 - Pre-capillary sphincters to relax
 - Reduced vascular resistance → More blood at greater pressure
 - Post-capillary venules endothelial cell to contract
 - Loosen junctions
 - Increase osmotic pressure within tissue space
 - Decrease osmotic pressure within vessels → BP drops
 - **Stasis**- temporary cessation of blood may occur

Mechanism of Inflammation

- Vaso dilatation
- Exudation - Edema
- Emigration of cells
- Chemotaxis
- The major local manifestations of acute inflammation, compared to normal.
 - Vascular dilation and increased blood flow (causing erythema and warmth).
 - Extravasation and deposition of plasma fluid and proteins (edema).
 - Leukocyte emigration and accumulation in the site of injury.

Changes in vascular flow

- Slowing of the circulation
 - Outpouring of albumin rich fluid into the extravascular tissues results in the concentration of RBCs in small vessels and increased viscosity of blood.
 - Leukocyte margination
 - Neutrophils become oriented at the periphery of vessels and start to stick.

Leukocyte cellular events

- Leukocytes leave the vasculature routinely through the following sequence of events:
 - Margination and rolling
 - Adhesion and transmigration
 - Chemotaxis and activation
- They are then free to participate in:
 - Phagocytosis and degranulation
 - Leukocyte-induced tissue injury

Margination

- With increased vascular permeability, fluid leaves the vessel causing leukocytes to settle-out of the central flow column and “marginate” along the endothelial surface
 - RBC clump in center of vessels when tissue inflamed; leukocytes forced to the outer walls of blood vessels

Rolling

- Endothelial cells and leukocytes have complementary surface adhesion molecules which briefly stick and release causing the leukocyte to roll along the endothelium like a tumbleweed until it eventually comes to a stop as mutual adhesion reaches a peak

Adhesion

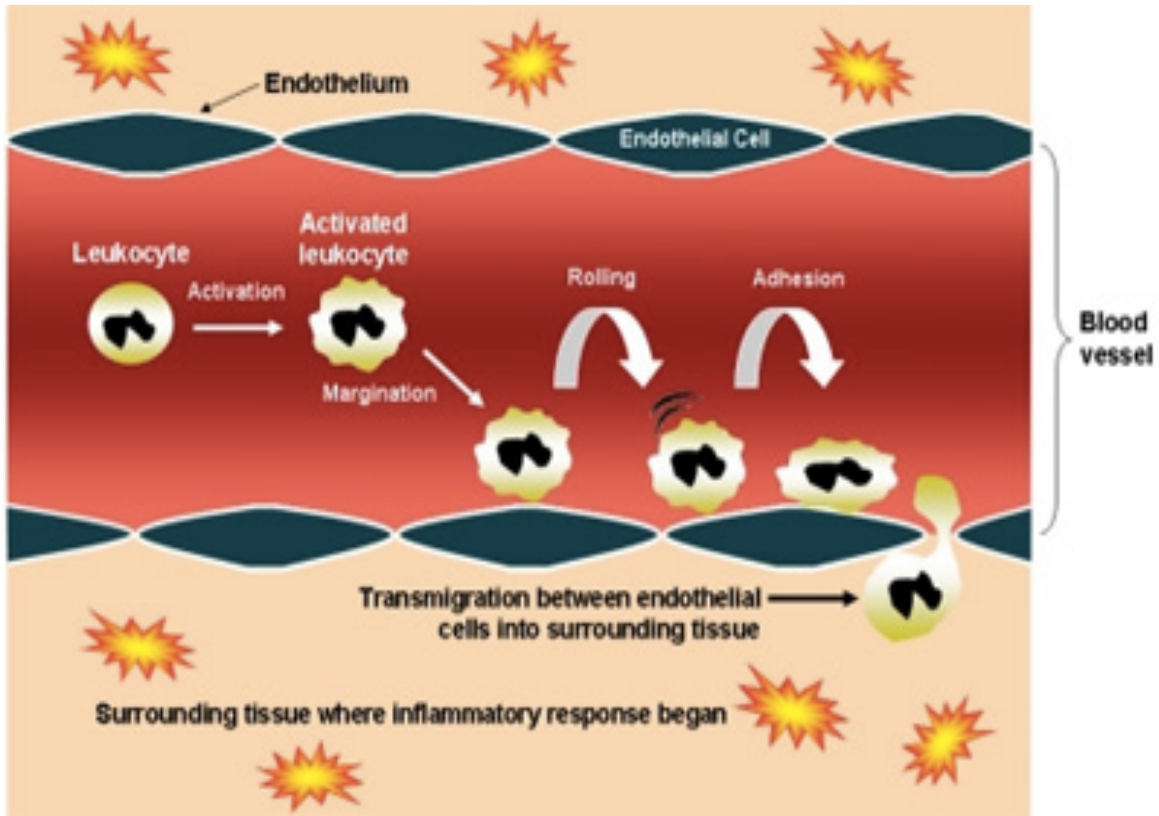
- Rolling comes to a stop and adhesion results
- Other sets of adhesion molecules participate:
 - Endothelial
 - Leukocyte
- Ordinarily down-regulated or in an inactive conformation, but inflammation alters this

Emigration

- Leukocytes “squeeze” through post-capillary venule endothelial cells
- First cells to emigrate are called polymorphonuclear cells (PMC)- include eosinophils and basophils
- Second cells to emigrate are called mononuclear cells- include monocytes and macrophages

Transmigration (diapedesis)

- Occurs after firm adhesion within the systemic venules and pulmonary capillaries.
- Early in inflammatory response mostly PMNs, but as cytokine and chemotactic signals change with progression of inflammatory response, alteration of endothelial cell adhesion molecule expression activates other populations of leukocytes to adhere (monocytes, lymphocytes, *etc*).



Benefits of Exudate

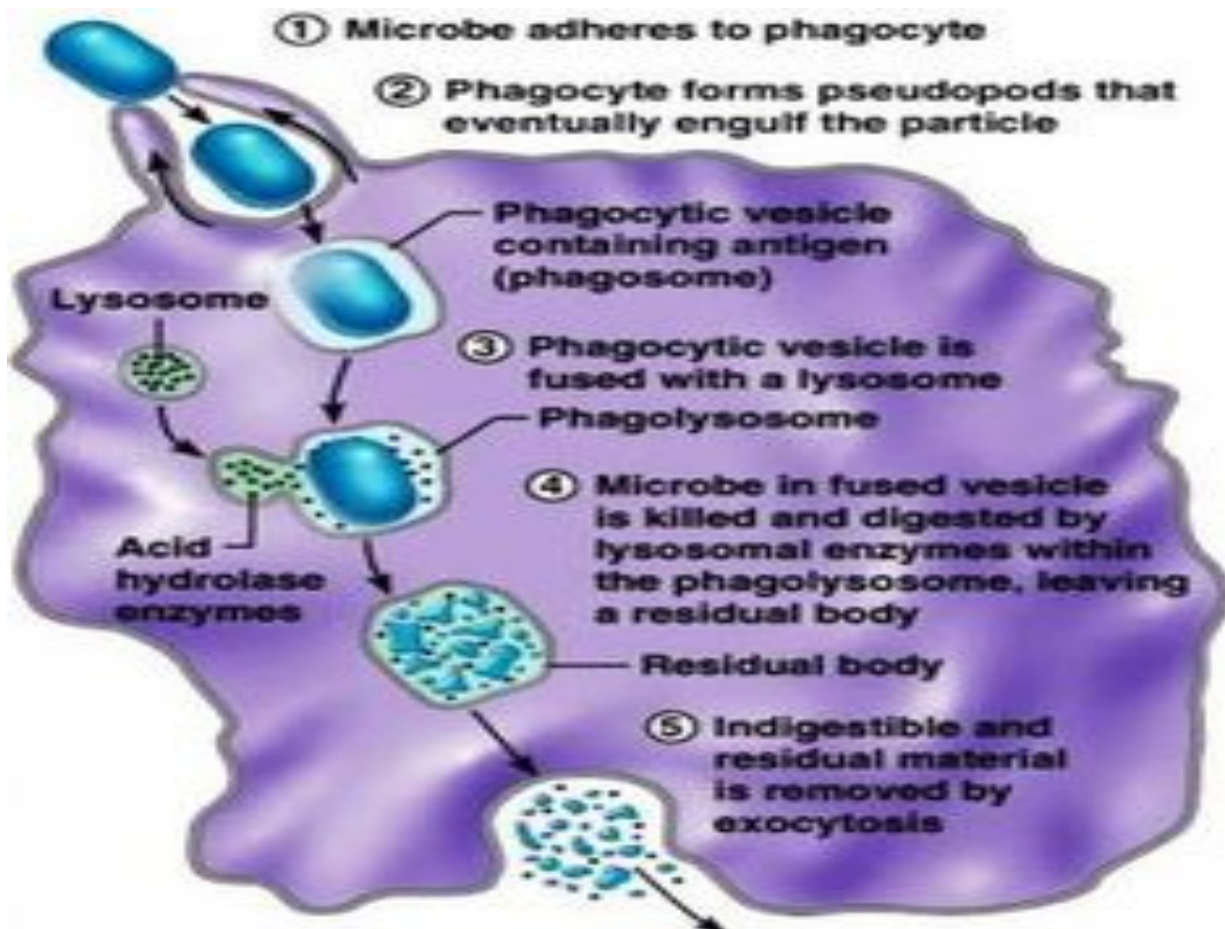
- Benefits of fluid and plasma protein accumulation at an injury site:
 - Dilution of toxins
 - Increased pain forces limits → prevents further injury
 - Presence of antibodies
 - More proteins amplify the response, kill organisms, and encourage phagocytosis of debris and microorganisms

Phagocytosis

- The process of phagocytic cells engulfing materials, such as...
 - Dead cells or cell components
 - Infectious agents
 - Immune complexes
- Phagocyte engulfs materials (endocytosis) and digests them (with lysosomal enzymes)
- **Chemotaxis**
 - The process of a phagocyte being attracted to an area of injury
 - Phagocytes have receptors for several chemicals (**chemoattractants**) found at sites of injury
 - Phagocytes follow concentration gradients of chemoattractants until they reach the site of injury

Phagocytosis

- Chemotaxis is enhanced by **opsonization**
 - **Opsonization** is a term that refers to an immune process where particles such as bacteria are targeted for destruction by an immune cell known as a phagocyte
 - The process of **opsonization** is a means of identifying the invading particle to the phagocyte.
 - Example of opsonin: pathogen-specific antibodies, C-reactive protein, C3b (a complement fragment), collectins (plasma proteins)
- **Engulfment**
 - When the phagocyte actually engulfs its target material(s)
 - Materials are exposed to the phagocyte's digestive enzymes
 - Killing of engulfed materials can be
 - **Oxygen-Independent** - many digestive enzymes damage bacterial cell walls, disrupt replication, and produce low pH
 - **Oxygen-Dependent** - release of oxygen free radicals that combine with halides and enzymes



Phagocytosis Defects

- **Chronic Granulomatous Disease of Childhood** - impaired oxygen-dependent phagocytosis (genetic)
- **Chédiak-Higashi Syndrome** - Defect in phagocyte motility and digestive ability (autosomal recessive)
- **Diabetes** - changes in blood vessel impair phagocytosis
- **Leukemia** - prevents mobilization of leukocytes from bone marrow
- **Some diseases** (arteriosclerosis, malnutrition) - compromised exudate formation
- **Many drugs** (morphine, steroids) - interfere with phagocyte function

Types of Acute Inflammation

- **Serous Inflammation**
 - Response to mild injuries
 - Exudate has much water, few proteins/cells → blisters
- **Purulent Inflammation**
 - Exudate has many leukocytes → pus
 - Involves pathogenic microbes and/or toxins
 - **Abscess** - Localized purulent inflammation
 - **Cellulitis** - Diffuse purulent inflammation
 - **Cyst** - threat removed, fluid-filled sac remains
- **Hemorrhagic Inflammation**
 - Injury is severe, capillary damage
 - Exudate has many RBC

Acute inflammation: Chemical Level

- Acute inflammation is non-specific
- **Initiators** - factors that can start the inflammatory response
 - Substances released from injured cells
 - Antigen-antibody complexes
 - Microbial products
- **Chemical mediators** - used by initiators to directly elicit vascular and cellular events of inflammatory response

Chemical Mediators

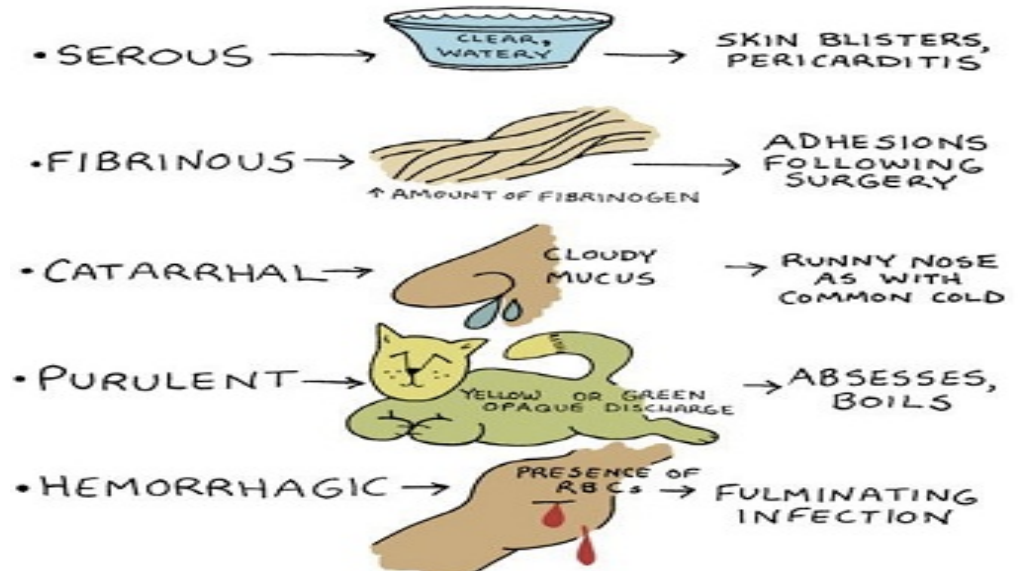
- Chemical substances synthesised or released and mediate the changes in inflammation.
 - *Histamine* by mast cells - vasodilatation.
 - *Prostaglandins* – Cause pain & fever.
 - *Bradykinin* - Causes pain.

Cell-Derived Chemical Mediators

- **Histamine**
 - Substance produced by mast cells and platelets in response to initiators
 - High concentration in loose CT supporting skin, GI tract mucosa, and respiratory tree
 - Leads to vasodilation, increase in vessel permeability
- **Nitric Oxide**
 - Important signal from macrophages
 - Vasodilator, anti-bacterial effect
- **Arachidonic Acid Derivative**
 - Formed from cell membrane phospholipids
 - Each has unique role in inflammatory response
 - Released by all leukocytes, especially mast cells
- **Corticosteroids**- shut off supply of arachidonic acid derivatives and shut down inflammation when it's out of control
- **Leukotrienes**
 - Some increase vascular permeability, produce vasoconstriction, and trigger bronchospasms
- **Prostaglandins and Thromboxanes**
 - Vasodilation and enhance effects of mediators
 - Blocked by the NSAIDs

Morphologic types of acute inflammation

- Exudative or catarrhal Inflammation: excess fluid
- Fibrinous – pneumonia – fibrin
- Membranous (fibrino-necrotic) inflammation
- Suppuration/Purulent – Bacterial - neutrophils
- Serous – excess clear fluid – Heart, lung
- Allergic inflammation
- Hemorrhagic – blood vessel damage
- Necrotising inflammation



Systemic Effects of Acute Inflammation

- Fever
- Loss of appetite
- Increase in deep sleep
- Weight loss
- Residual weakness
- **Lymphadenitis**- swollen lymph nodes
- **Bacteremia**- bacteria pass into the blood
- **Leukocytosis**- 2-3 fold increase in circulating leukocytes
 - **Differential white cell counts** helpful in diagnosis

Anti-inflammatory therapy

- Anti-inflammatory therapy
 - Problems can arise from excessive inflammation
 - Excessive swelling impairs function
 - Extreme pain
 - Excessive tissue damage
 - Apply cold to reduce swelling
 - (Later) Apply heat to stimulate phagocytosis
 - Elevate swollen extremities (promotes drainage)
 - Administer drugs (e.g. antihistamines, steroids)

Acute inflammation has one of four outcomes:

- Abscess formation
- Progression to chronic inflammation
- Resolution--tissue goes back to normal
- Repair--healing by scarring or fibrosis

Chronic inflammation

- Lymphocyte, macrophage, plasma cell (mononuclear cell) infiltration
- Tissue destruction by inflammatory cells
- Attempts at repair with fibrosis and angiogenesis (new vessel formation)
- When acute phase cannot be resolved
 - Persistent injury or infection (ulcer, TB)
 - Prolonged toxic agent exposure (silica)
 - Autoimmune disease states (RA, SLE)

The Players (mononuclear phagocyte system)

- Macrophages
 - Scattered all over (microglia, Kupffer cells, sinus histiocytes, alveolar macrophages, etc.
 - Circulate as monocytes and reach site of injury within 24 – 48 hrs and transform
 - Become activated by T cell-derived cytokines, endotoxins, and other products of inflammation

The Players (mononuclear phagocyte system)

- T and B lymphocytes
 - Antigen-activated (via macrophages and dendritic cells)
 - Release macrophage-activating cytokines (in turn, macrophages release lymphocyte-activating cytokines until inflammatory stimulus is removed)
 - Produce antibodies
- Eosinophils
 - Found especially at sites of parasitic infection, or at allergic (IgE-mediated) sites

Granulomatous Inflammation

- Clusters of T cell-activated macrophages, which engulf and surround indigestible foreign bodies (mycobacteria, *H. capsulatum*, silica, suture material)
- Resemble squamous cells, therefore called “epithelioid” granulomas

Patterns of acute and chronic inflammation

- Serous
 - Watery, protein-poor effusion (e.g., blister)
- Fibrinous
 - Fibrin accumulation
 - Either entirely removed or becomes fibrotic
- Suppurative
 - Presence of pus (pyogenic staph spp.)
 - Often walled-off if persistent
- Ulceration
 - Necrotic and eroded epithelial surface
 - Underlying acute and chronic inflammation
 - Trauma, toxins, vascular insufficiency

Systemic effects

- Fever
 - One of the easily recognized cytokine-mediated *acute-phase reactions* including
 - Anorexia
 - Skeletal muscle protein degradation
 - Hypotension
- Leukocytosis
 - Elevated white blood cell count
 - Bacterial infection (neutrophilia)
 - Parasitic infection (eosinophilia)
 - Viral infection (lymphocytosis)

