Inflammation

A normal response of living tissues to injury. It prepares the tissue for healing and repair.
Inflammation

- The body’s response to injury of vascularized tissue with a series of events, collectively called inflammation and repair.

- Ultimate goal is to replace injured tissue
Inflammation

Types of Injuries

- trauma
  - crush, applied force, sharp object, etc..

- anoxia
  - may be due to trauma, may be due to other factors that impair blood supply

- poison
  - ingested, “infection”, venom
Inflammation

- A dynamic process that lasts from a few minutes to a few years. Depending on:
  - the extent of the injury
  - the type of injury
  - the vascularity of the tissue
Inflammation

- Protective Role
  - Although inflammation is a necessary process, it must be contained.
  - It serves to inform the individual that an area has been injured.
  - It restricts function to prevent further injury to the area.
Cardinal Signs of Inflammation

- Erythema
- Heat production
- Edema
- Pain
- Loss of Function
Inflammation

- The presence of the cardinal signs of inflammation provide the observant clinician with information regarding the acuity of the injury.

  "The more cardinal signs of inflammation present, the more acute the problem."
Functions of Inflammation

- Inactivate injurious agent
- Break down and remove dead tissue
- Initiate healing of tissue
Inflammatory Response

Complex response that involves:
- circulatory (hemo-dyanamic) changes
- changes in vessel wall permeability
- response of white blood cells
- release of soluble mediators
Circulatory (Hemodynamic) Changes

- body’s first response to injury
  - a mechanical stimulus causes the nerves that transmit signals to smooth muscle cells on precapillary arterioles.
  - Smooth muscle cells act as sphincters, regulating the inflow blood into the capillaries.
  - Relaxation of smooth muscle cells allows blood to rush into the capillaries
    - erythema, edema, and heat
Circulatory (Hemodynamic) Changes

- first response of arterioles to injury…
  - vasoconstriction (a few seconds in duration)
- Followed by…
  - vasodilation
  - flooding the capillary network with arterial blood
- Blood influx into the area
  - dilates capillaries (endothelial cells & basement membrane)
    - blood flow is not effectively regulated
Circulatory (Hemodynamic) Changes

- Pressure from the capillaries is transmitted to the venules
  - Have no capacity to contract
- Increased pressure in the capillaries and venules forces:
  - Plasma filtration through the vessel wall
    - Results in: Edema formation
Circulatory (Hemodynamic) Changes

- Dilated Capillaries & Venules
  - slowed blood flow
  - leads to congestion
  - sludged, erythrocytes form stacks = rouleaux
    - impair circulation further
Circulatory (Hemodynamic) Changes

- Leukocytes (WBC) marginalize
  - become attached to the endothelium
    - “pavementing”
- Leukocytes develop elongated protrusions of the surface cytoplasm, become sticky
  - adhere to the endothelial cells lining the capillaries (particularly those in the postcapillary venules)
Circulatory (Hemodynamic) Changes

- WBC adhesion to the surface of the venules accomplished by surface adhesion molecules
  - normally present on leukocytes and endothelial cells in an inactive form
  - during inflammation, activated by soluble mediators of inflammation
    - interleukins
Circulatory (Hemodynamic) Changes

- Interleukins
  - A type of cytokine (protein)
    - derived from platelets and leukocytes
  - Normally present in blood in small amounts
    - Concentrations increase at site of inflammation
  - Mediate communication among leukocytes and other cells active in inflammation or cell mediated immune response
  - The result is a maximized response to a microorganism or other foreign antigen.
Circulatory (Hemodynamic) Changes

- Adhesion of leukocytes to the endothelial cells is one of the most common triggers for the release of mediators of inflammation.
- Platelets initiate clotting, which leads to the formation of fibrin strands.
- Fibrin strands “anchor” the leukocytes to the vessel wall and prevent them from moving away.
Changes in Vessel Wall Permeability

- Occurs in capillaries and postcapillary venules

- Changes occur due to
  - increased pressure inside the blood vessels
  - slowed circulation
    - reduction in the oxygen supply and nutrients to endothelial cells
  - adhesion of leukocytes and platelets to endothelial cells
  - release of soluble mediators of inflammation from inflammatory cells
Mediators of Inflammation

- Chemical Mediators
  - Plasma derived
    - circulate in an inactive form
    - must be transformed into an active form by an activator
      - numerous, specific and non-specific
      - all activators have natural in-activators to maintain balance
  - Cell derived
    - may be pre-formed and stored in granules of platelets and leukocytes (histamine)…or…
    - may be synthesized as needed
Mediators of Inflammation

Multi-functional

numerous effects on:
- the blood vessels
- inflammatory cells
- other cells in the body
Mediators of Inflammation

- effects include
  - vasodilation
  - vasoconstriction
  - altered vascular permeability
  - activation of inflammatory cells
  - chemotaxis
  - cytotoxicity
  - degradation of tissue
  - pain
  - fever
Mediators of Inflammation

- Biogenic amines
  - Histamine
- Peptides
  - Bradykinin
  - Complement system
- Arachadonic acid derivatives
  - Prostaglandins
Mediators of Inflammation

- **histamine**
  - released from mast cells, basophils and platelets
  - cause a contraction of the endothelial cells of venules
    - gaps form, increasing vessel permeability
    - fluids and blood cells exit into interstitial space
  - effect rapidly inactivated by histaminase
Mediators of Inflammation

- bradykinin
  - Plasma protein formed through the activation of a coagulation factor (XII)
  - leads to the activation of several biological systems in the circulating blood
    - act on the blood vessel wall
    - inflammatory cells
      - sustain and amplify the response to injury
    - incites pain perception (cardinal sign)
  - Effects similar to histamine
Mediators of Inflammation

Arachadonic Acid Derivatives
- derived from the phospholipids of cell membranes
- Involved in all stages of inflammation
- Once arachadonic acid derivatives are formed, further metabolized by 1 of 2 pathways
Mediators of Inflammation

- Arachidonic Acid Derivatives
  - lipoxigenase pathways - leukotrine formation
    - active in chemotaxis
    - increase vascular permeability
    - AKA slow-reacting substances of anaphylaxis
      - cause bronchospasm in asthma by contraction of the smooth muscles in the bronchi
      - Cause anaphylactic shock by contraction of the smooth muscles in the bronchi
Mediators of Inflammation

- Arachidonic Acid Derivatives
  - cyclooxygenase pathway (COX)
    - formation of prostaglandins
      - Modulate vasomotor tone
      - modulate platelet aggregation and thrombosis
      - promote pain perception and mediate fever
Inflammation and Medications

- **NSAIDs**
  - blocks prostaglandin synthesis
  - Aspirin or COX-2 inhibitors

- **Corticosteroids**
  - inhibit arachidonic acid formation
  - BLOCKS BOTH PATHWAYS
Cellular Events in Inflammation

- Increased permeability of the vessel walls of postcapillary venules and capillaries.
  - Leakage of fluid from the vessels into the interstitial spaces.
    - "transudation"
      - Edema formation
Transudate

- contains few cells
- readily exchanges across vessel walls
- clear
- thin
Cellular Events in Inflammation

- When cells actively cross the vessel walls, exudate is formed
  - contains more protein than transudate
  - contains inflammatory cells
    - In acute phase, most are polymorphonuclear leukocytes (PMNs)
Polymorphonuclear Leukocytes

- 60-70% of all WBCs
- 2-4 day lifespan
- first to appear in acute inflammation
- highly mobile
- bacteriocidally active
- perform phagocytosis
- produce and release mediators of inflammation
  - cytokines
    - interleukin-1.....a pyrogen that acts on the hypothalamus......causes fever
Polymorphonuclear leukocytes

- As inflammation evolves, PMNs are joined by monocytes and eosinophils (within 48 hrs)
- As inflammation progresses into chronic phase, PMNs are replaced by macrophages, lymphocytes, and plasma cells
The Inflammatory Process

- adhesion of PMNs to the endothelial cells
  - insertion of cytoplasmic pseudopods between the junctions of endothelial cells
- passage through the basement membrane
- ameboid movement away from the vessel toward the cause of inflammation (chemotaxis)
The Inflammatory Process

- Phagocytosis
  - PMNs reach the bacteria or irritant
    - lose mobility
    - begin acting as scavengers
      - active uptake of bacteria or other cellular debris
      - lysosomal degranulation of irritant
  - PMNs die in the process
    - released in a yellow viscous fluid
      - pus (purulent)
Cells of Inflammation

- **Eosinophils**
  - 2-5% of WBCs
  - appear 2-3 days after the PMNs
  - slower to react, slower mobility
  - single nucleus
  - prominent in allergic reactions
    - hay fever, asthma
    - parasitic infections
  - live longer than PMNs, are present in chronic inflammation
Cells of Inflammation

- **Basophils**
  - less than 1% of WBCs
  - most prominent in allergic reactions regulated by immunoglobulin E
  - rich in vasoactive substances
    - histamine
  - precursors of mast cells
Cells of Inflammation

- Macrophages
  - tissue cells (histocytes)
  - appear 3-4 days after infection or tissue destruction
  - long lifespan, present in chronic inflammation
  - capable of phagocytosis
  - rich in lytic enzymes
  - secrete cytokines locally and systemically
  - recruit lymphocytes to site of inflammation
Macrophages

- produce
  - lymphocyte growth factors
  - fibroblast growth factors
  - arachidonic acid metabolites

- activate
  - coagulation sequence
  - thrombolysis
Cells of Inflammation

- lymphocytes
  - main means of providing the body with immunity
  - 20-40% of the WBCs
  - activated by the presence of a specific antigen
Cells of Inflammation

- platelets
  - fragments of cytoplasm released from bone marrow
  - no nucleus
  - cytoplasm contains vacuoles with 3 types of granules
    - dense granules, rich in histamine and ADP
    - alpha granules, rich in coagulation proteins
    - lysosomes, rich in enzymes
Cells of Inflammation

- **Platelets**
  - release their granules upon contact with
    - extracellular matrix
    - endothelial cells
    - thrombin formed in early thrombi
  - release of histamine increases vascular permeability during the early stages of inflammation
  - promote the proliferation of connective tissue cells
Classification of Inflammation in Clinical Practice

Classification based on
- duration
- etiology
- location
- morphology or pathological characteristics
Classification of Inflammation

- **Duration**
  - “Acute Inflammation”
    - lasts from a few hours to a few days
    - Sudden onset, short duration, severe symptoms
    - (possesses the cardinal signs of inflammation
      - heat, erythema, edema, pain, loss of function)
    - Recurrent- acute inflammation that occurs in bouts
Classification of Inflammation

- **Chronic Inflammation**
  - Represents:
    - extension of an acute inflammation
    - prolonged healing of an acute inflammation
    - persistence of causative agents
  - May evolve without acute phase
    - TB has gradual onset and lasts a long time. Frequently cannot pinpoint exact onset of symptoms or remember acute phase
  - Can have acute exacerbation of chronic problem
Classification of Inflammation

- Chronic inflammation
  - may develop in response to a foreign substance
  - foreign body granulomas develop around a objects in subcutaneous tissues
Classification of Inflammation

- Duration
  - Acute
    - PMNs regulated
  - Chronic
    - Macrophages, lymphocytes, and plasma cells

***Much too simplistic***
Classification of Inflammation

- **Etiology**
  - “The study of the causes of disease.”
  - Inflammations are caused by
    - infectious pathogens
    - chemical
    - physical
    - immune factors
Infections are caused by
- bacteria
- viruses
- protozoans
- fungi
- helminthic origins (wormlike animals)
Etiology

- chemical causes
  - organic / inorganic
  - industrial / medicinal
  - exogenous / endogenous

- physical causes
  - foreign bodies
  - heat
  - irradiation
  - trauma
Etiology of Inflammation

- Many inflammations are multi-factorial
  - infectious inflammations
    - chemicals released from the pathogens or chemical mediators released from inflammatory cells.
    - may elicit an immune response
      - may cause pathogenesis of tissue damage
Classification of Inflammation

Location

- Localized

- Widespread or Systemic
  - involving multiple organs
  - bacteria spread throughout the blood stream
Classification of Inflammation

- Pathological Characteristics
  - Serous
    - clear exudate (blisters)
    - acute inflammatory response
    - Mildest form of inflammation
Classification of Inflammation

Pathological Characteristics

- Fibrinous
  - exudate rich in fibrin
  - Relatively severe inflammation
  - Common with bacterial infections
Classification of Inflammation

Pathological Characteristics

- Purulent
  - pus formation
  - Can occur on mucosa, skin…or
  - In internal organs
    - abscess
Tissue Healing & Repair

- Injury
- Inflammation
- Debridement
  - removal of necrotic tissues
- Repair
- Remodeling
Inflammation

- Tissues that can regenerate themselves:
  - skin
  - muscle
  - peripheral nerves
  - bone

- Tissues that CANNOT regenerate themselves:
  - brain, spinal cord
Tissue Repair

- Participating Cells
  - leukocytes
  - macrophages
  - connective tissue cells
  - epithelial cells
  - myofibroblasts
    - allow epithelial cells to cover the surface defect
  - angioblasts
    - precursors to blood vessels
Tissue Repair

- fibroblasts
  - produce most of the extracellular matrix
  - fibronectin
    - “glues” cells together
  - collagen
    - forms fibrin strands which provide tensile strength
Remodeling

- newly manufactured tissue is remodeled in response to the stresses placed upon it.

- healing by first intention
  - renewal of epithelium and approximation of the underlying tissue
    - sterile or surgical wound healing

- healing by second intention
  - process of tissue repair from the base of the wound up
    - Large defects or infected wounds
    - Prolonged
Remodeling

- Granulation tissue
  - Temporary structure that changes over time
  - Vascularized connective tissue
Wound healing

Scar tissue

- replaces damaged tissue that cannot regenerate
  - restores structural integrity
  - HOWEVER, it is only about 70-80% of the tensile strength of normal tissue
  - it is poorly vascularized
  - may disrupt organ function
  - may restrict movement
  - may be disfiguring
Delays in Wound Healing

- site
  - some tissues heal well, others do not
- mechanical factors
  - juxtaposition of the borders, tension, foreign particles
- size
- infection
- circulatory status
- nutrition
- age of the patient
- medications
Complications of Wound Healing

- Deficient Scar Formation
  - Sluggish formation of granulation tissue
  - Inadequate collagen production
  - Results in poor tensile strength

- Excessive Scar Formation
  - Hypertrophic scars (keloid)
    - Defective remodeling of scar tissue
  - Large irregularly shaped scars near a joint
    - May lead to contractures, impeding ROM
    - Burns