1) Inflammation
   a) Define and distinguish between acute and chronic

2) Acute Inflammation
   a) Vascular events
   b) Cellular events
   c) Mediators of inflammation
   d) Possible outcomes of inflammation

3) Chronic Inflammation
   a) Cellular events
   b) Granulomatous inflammation

4) Patterns of Acute and Chronic Inflammation

5) Clinical picture

6) Tissue Injury and Repair
   a) Granulation tissue
   b) Clinical wound healing
1. Inflammation

- *Inflammatio* (L) - “to set on fire”
- “-itis” e.g., appendicitis, pancreatitis, meningitis, arthritis
Inflammation

- provoked response to tissue injury
  - chemical agents
  - cold, heat
  - trauma
  - invasion of microbes
- protective: destroys, dilutes or contains the injurious agent
- reparative: induces and supports tissue repair
- potentially harmful (e.g., arthritis)
Acute versus chronic inflammation are distinguished by duration and type of infiltrating inflammatory cells.
2. Acute inflammation

**Steps of the Inflammatory Response**

The inflammatory response is a body's second line of defense against invasion by pathogens.

1. Damaged tissues release histamines, increasing blood flow to the area.
2. Histamines cause capillaries to leak, releasing phagocytes and clotting factors into the wound.
3. Phagocytes engulf bacteria, dead cells, and cellular debris.
4. Platelets move out of the capillary to seal the wounded area.
CARDINAL SIGNS OF ACUTE INFLAMMATION

Heat       Redness    Swelling       Pain     Loss of function

Celsius – (30 BC)   Galen – (100 AD)
Acute Inflammation Components

Physiological Responses
- Release of soluble mediators
- Vasodilation
- Increased blood flow
- Extravasation of fluid (permeability)
- Cellular influx (chemotaxis)

Symptoms
- Heat (calor)
- Redness (rubor)
- Swelling (tumor)
- Pain (dolor)
Acute Inflammation Components

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- Swelling *(tumor)*
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Acute Inflammation Components

Physiological Responses
- Release of soluble mediators
- Vasodilation
- Increased blood flow
- Extravasation of fluid (permeability)
- Cellular influx (chemotaxis)

Symptoms
- Heat (calor)
- Redness (rubor)
- Swelling (tumor)
- Pain (dolor)
• Physiological responses (2 components):

  – Vascular
    • Vasodilation and Vascular leakage (edema)

  – Cellular
    • Leukocyte infiltration
2a) Vascular Events

- First, there may be a brief (few seconds) arteriolar vasoconstriction (e.g., blanching after a burn or scrape) mediated by autonomic nerves or direct injury to arteriolar smooth muscle wall.

- Second, smooth muscle relaxes and vasodilation follows.
  - This vasodilatory smooth muscle response is termed active hyperemia.*

*increase in organ blood flow
Active Hyperemia

- **Vasodilation**
  - Arteriolar smooth muscle cells relax, precapillary sphincter opens and blood flow increases (**active hyperemia**)
  - Accounts for tissue redness, swelling and warmth
  - Increased intravascular pressure causes an early **transudate** (protein-poor filtrate of plasma) to pass into interstitium
  - Blood flow in dilated capillaries and venules slows (**congestion**)

*Figure 2-2*
Circulatory changes in inflammation. Relaxation of the precapillary sphincter in the arterioles results in flooding of the capillary network and dilatation of capillaries and postcapillary venules.
Active Hyperemia

- Vascular permeability (leakiness) commences
  - Transudate gives way to exudate (protein-rich) which increases interstitial osmotic pressure
  - Exudate supplies antibodies and complement to the affected area
  - Increased interstitial osmotic pressure contributes to swelling/edema and lymphatic collapse (poor drainage)
  - Swelling can be beneficial
    - Causes pain (dolor) so limits mobility around the affected area (i.e., loss of function)

![Figure 2-2](https://via.placeholder.com/150)

*Circulatory changes in inflammation. Relaxation of the precapillary sphincter in the arterioles results in flooding of the capillary network and dilatation of capillaries and postcapillary venules.*
Vascular leakage

- **Five mechanisms** known to cause vascular leakiness and all or any combination of these events may occur in response to a given stimulus

1) Histamines, bradykinins, leukotrienes cause an early, brief (15 – 30 min.) *immediate transient response* in the form of **reversible** endothelial cell contraction that *widens* intercellular gaps of *venules* (not arterioles or capillaries)
Vascular leakage

2) Cytokine mediators (TNF, IL-1) induce:
- reversible *endothelial cell junction retraction* through cytoskeleton reorganization (4 – 6 hrs post injury, lasting 24 hrs or more)

3) Severe injuries may cause:
- immediate *direct endothelial cell damage* (necrosis, detachment) making them leaky until they are repaired (*immediate sustained response*)
- delayed damage as in thermal or UV injury (sunburn) or some bacterial toxins (*delayed prolonged leakage*)
Vascular leakage

4) Leukocytes may adhere to and damage the endothelium through activation and release of toxic oxygen radicals and proteolytic enzymes (leukocyte-dependent endothelial cell injury) making the vessel leaky
Vascular leakage

5) Certain mediators (e.g., VEGF released by neutrophils and platelets) may increase transcytosis...intracellular vesicles extend from the luminal surface to basal lamina surface of the endothelial cell.
Stasis

Loss of fluid from vasculature:

- Red blood cells concentrate (rouleaux)
- Blood viscosity increases
- Circulation around the affected area slows down (stasis)
- As blood viscosity increases, leukocytes accumulate (marginate) along the vessel wall
2b) Cellular events

- Diapedesis:
  - Leukocytes leave the vasculature and enter the interstitium through the following sequence of events:
    - Margination and rolling
    - Adhesion and transmigration
    - Chemotaxis and activation

- Leukocytes are then free to participate in:
  - Phagocytosis and degranulation
  - Leukocyte-induced tissue injury
Blood Cell Lineage
Cells of Inflammation

• Polymorphonuclear leukocyte (Neutrophil)
  – 60-70% of circulating white blood cells (WBCs)
  – Polymorphic nucleus (multi-lobed)
  – Neutrophil granules stain light pink with hematoxylin and eosin (neutral pink → neutrophil; dark blue → basophil; bright red → eosinophil)
  – Characteristics
    • Highly mobile (ameboid)
    • Bactericidal (kills)
    • Phagocytic (scavenges)
    • Source of mediators (stored and newly synthesized)
Cells of Inflammation (cont’d)

- Monocyte/Macrophage
  - 2-8% of circulating WBCs
  - Bean- or horseshoe-shaped eccentric nucleus
  - Characteristics
    - Long lived
    - Increased presence in Chronic Inflammation
    - Cytokine secretion
Cells of Inflammation (cont’d)

• Eosinophil
  – 2-3 % of circulating WBCs
  – Bilobed nucleus
  – Granules stain with eosin
  – Characteristics
    • Similar to those of the neutrophil, but no role against bacteria
    • Appear 2-3 days after neutrophils
    • Prominent role in allergic reactions (high affinity receptors for IgE and C3b complement)
    • Evolved to attack IgE- and C3b-coated parasites (e.g., helminths like schistosomula)
    • Eosinophil peroxidase and major basic protein can contribute to local pathology (asthma and inflammatory bowel disease)
Cells of Inflammation (cont’d)

• Basophil
  – <1% of circulating WBCs
  – Bean-shaped nucleus
  – Granules stain with basic dyes
  – Characteristics
    • Share characteristics with mast cells (granules contain histamine and heparin; can produce leukotrienes)
    • Prominent role in allergic reactions (high affinity receptors for IgE)
    • Granules also contain eosinophil chemotactic factor (ECF-A) which attracts eosinophils
Cells of Inflammation (cont’d)

- **Platelets**
  - 150,000-450,000 per ul (microliter) of blood
  - Produced from megakaryocytes in bone marrow
  - No nucleus; 2-3 um in diameter

- **Characteristics**
  - Primary function is hemostasis (thrombus formation)
  - Granules contain histamine, coagulation proteins, cytokines, growth factors (PDGF, platelet-derived growth factor)
  - Granules are released upon activation caused by platelet binding to endothelium or exposed extracellular matrix
Cells of Inflammation (cont’d)

• Other cells*
  – Lymphocytes
    • 20-30% of circulating WBCs
    • T and B cells
  – Plasma cells
    • Derived from B cells
    • Produce Antibody

* Characteristic of Chronic Inflammation and these cells have an immune response that will be described in “great” detail by Dr. Redfern
Leukocyte Recruitment at Inflammatory Sites
Neutrophil Recruitment on IL-1-activated human endothelium
Transmigration

• facilitated by endothelial adhesion molecules (PECAM, JAMs, CD99)
Chemotaxis

- Leukocytes follow chemical gradient to site of injury (chemotaxis)
  - Soluble bacterial products
  - Complement components (C5a)
  - Chemokines (e.g., IL-8)
  - LTB$_4$ (AA metabolite)

- Chemotactic agents bind surface receptors inducing calcium mobilization and assembly of cytoskeletal contractile elements......i.e., leukocyte activation
Crawling Neutrophil Chasing a Bacterium

- 1950’s 16mm movie by the late David Rogers at Vanderbilt University
- Neutrophil chasing *Staphylococcus aureus*
- Chemoattractant unknown but:
  - bacterial N-formyl peptides are directly chemotactic for neutrophils
Bacterial Killing

- **Opsonins**: facilitate leukocyte adhesion to bacterium (IgG antibody and C3b)

- **Oxygen-dependent killing**: Engulfment of bacterium by phagocytic vacuole is associated with a chemical reaction (respiratory burst) driven by NADPH oxidase

- **Oxygen-independent killing**: Fusion of phagocytic vacuole with lysosomes and cytoplasmic granules containing hydrolytic enzymes
Oxidative burst

- Reactive oxygen species (ROS) formed through oxidative burst involving:
  - Increased oxygen consumption
  - Glycogen → glucose
  - Glucose oxidation

- Examples of ROS:
  - Superoxide anion
  - Hydrogen peroxide
  - Hypochlorous acid
  - Hydroxyl radical

\[ \text{H}_2\text{O}_2 + \text{Fe}^{2+} \rightarrow \cdot\text{OH} + \text{OH}^- + \text{Fe}^{3+} \]

\[
\begin{align*}
2\text{O}_2 + \text{NADPH} & \xrightarrow{\text{oxidase}} 2\text{O}_2 \cdot^- + \text{NADP}^+ + \text{H}^+ \\
2\text{O}_2 \cdot^- + 2\text{H}^+ & \xrightarrow{} \text{H}_2\text{O}_2 + \text{O}_2 \\
\text{H}_2\text{O}_2 + \text{H}^+ & \xrightarrow{\text{myeloperoxidase} + \text{chloride ion}} \text{HOCl} + \text{H}_2\text{O} \\
2\text{O}_2 \cdot^- & = \text{superoxide anion radical} \\
\text{H}_2\text{O}_2 & = \text{hydrogen peroxide} \\
\text{HOCl} & = \text{hypochlorous acid} \\
\cdot\text{OH} & = \text{hydroxyl radical}
\end{align*}
\]
Reactive oxygen species

- Hydrogen peroxide alone is insufficient

- Myeloperoxidase (MPO), contained in neutrophil azurophilic granules, converts hydrogen peroxide to hypochlorous acid (HOCl\(^{-}\)), an oxidant/antimicrobial agent
Degradation and Clean-up

- Reactive end-products only active within phagolysosome
- Dead microorganisms degraded by lysosomal acid hydrolases
- Hydrogen peroxide broken down to water and oxygen by catalase
Leukocyte granules

• Other antimicrobials in leukocyte granules:
  – Bactericidal permeability increasing protein (BPI)
  – Lysozyme
  – Lactoferrin
  – Defensins (cationic proteins that punch holes in membranes)

---

**Oxygen independent**
- Cationic proteins
- Lactic acid
- Lactoferrin
- Lysozyme
- Proteolytic enzymes

**Oxygen dependent**
- Superoxide anion
- Hydrogen peroxide
- Hypochlorous
- Hydroxyl radical

**Fig 3-9** Killing by phagocytes.
Leukocyte-induced tissue injury

• Destructive enzymes can enter extracellular space if:
  – Premature degranulation
  – Frustrated phagocytosis (large, flat)
  – Membranolytic substances (urate crystals)
  – Persistent leukocyte activation (rheumatoid arthritis, emphysema)
2c) Mediators of Inflammation
Mediator Systems

i) Vasoactive amines

- **Histamine**: vasodilation and venular endothelial cell contraction, junctional widening

- Released by **mast cells**, basophils, platelets in response to:
  - injury (trauma, heat)
  - immune reactions (IgE-mast cell FcR)
  - anaphylatoxins (C3a, C5a fragments)
  - cytokines/chemokines (IL-1, IL-8)
  - neuropeptides
  - leukocyte-derived histamine-releasing peptides

- Histamine-induced increase in vascular permeability lasts <30 minutes; inactivated by eosinophil histaminase; **immediate transient reaction**
Mast cells at the limbus
- **Serotonin**
  - vasodilatory effects similar to histamine
  - found in platelet dense-body granules
  - release triggered by platelet aggregation and platelet activating factor (PAF)
Mediator Systems

ii) Plasma Protein Systems

• Clotting factors
Hemostasis: Vasoconstriction & Plug (Loose Clot) Formation

- Vasoconstriction
- Platelet activation
  - Multiple factors
  - Positive feedback
- Aggregation
- Loose plug
Coagulation (Clot Stabilization)

![Diagram of coagulation process]

- Fibrinogen
- Fibrin monomers
- Fibrin polymers
- Thrombin
- Fibrinopeptides
  - A
  - B
- Fibrin monomer
- Fibrin dimer
- Fibrin polymer

The process involves the conversion of fibrinogen to fibrin monomers, which then polymerize into fibrin polymers under the action of thrombin.
Coagulation Pathways

Contact Activation Pathway

All clotting factors are made in the liver except Factors III, IV, VIII

Tissue Factor Pathway
Dissolving the Clot

- Bleeding stopped
- Vessel repair
- Plasmin
- Fibrinolysis
- Clot dissolved
• Bradykinin
  – Formed from inactive precursors
  – Venular permeability increases
  – Arteriolar dilation
  – Causes pain (Dolor)
  – Rapidly inactivated (kininases)
FIGURE 2-15 Interrelationships between the four plasma mediator systems triggered by activation of factor XII (Hageman factor). Note that thrombin induces inflammation by binding to protease-activated receptors (principally PAR-1) on platelets, endothelium, smooth muscle cells, and other cells. HMWK, high molecular weight kininogen.
Complement system ~20 interactive plasma and cell membrane components

• “Complements” antibody killing of bacteria

• However, antibodies are not necessary for complement activation and bacterial killing
Complement system
- 3 pathways

- Antigen:antibody complexes (pathogen surfaces)
- Mannose-binding lectin binds mannose on pathogen surfaces
- Pathogen surfaces
Classical Complement Pathway

- Triggered by antibodies or C-reactive protein binding to foreign cells. C-reactive protein is made in the liver and reacts with a Pneumococcal carbohydrate antigen.

Over a decade ago, it was decided the smaller of all C fragments should be designated with an "a", the larger with a "b". This required changing the existing nomenclature for C2. That is why you will find the C3 convertase designated C4b2a in older literature [and C4b2b in newer literature].
Alternative Complement Pathway

- Triggered by C3b binding to bacterial cell wall (e.g., LPS). While antibody is not required, this pathway can be triggered by IgG and IgA aggregates.

- Alternative pathway Factor B combines with cell-bound C3b to form C3bB

- Factor D splits Factor B into Bb and Ba, forming C3bBb

- A serum protein called properdin (Factor P) binds and forms C3bBbP which functions as C3 convertase

\[
\text{“Spontaneous”} \\
\text{C3 + water} \rightarrow \text{C3a + C3b}
\]
Classical and Alternative Complement Pathways trigger C3 cleavage. C3 is the most pivotal and abundant complement component.
Cytolysis Caused by Membrane Attack Complex

1. Antibody molecules attach to antigens on pathogen’s plasma membrane.
2. Complement proteins link two antibody molecules.
4. MAC pores in the membrane cause cell lysis.

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Alternative pathway doesn’t require C1, C2 or C4, or specific antibody. Hence, the alternative pathway is of greater importance than the classical pathway in the initial defense against infection.
A third pathway is the Lectin Pathway

Mannose binding lectin (MBL)
### Summary of Complement Activation:

<table>
<thead>
<tr>
<th>Complement component</th>
<th>Biologic activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3a (an anaphylatoxin)</td>
<td>Triggers mast cell degranulation and increases vascular permeability</td>
</tr>
<tr>
<td>C3b</td>
<td>Opsonin—recognizes receptors on PMNs, macrophages, eosinophils</td>
</tr>
<tr>
<td>C4a (an anaphylatoxin)</td>
<td>Same activity as C3a but is probably less important</td>
</tr>
<tr>
<td>C5a (an anaphylatoxin)</td>
<td>Same activity as C3a. In addition, it is an important chemotactic factor for PMNs, monocytes, eosinophils, and basophils</td>
</tr>
<tr>
<td>C5b–C9</td>
<td>Membrane attack complex—produces lysis of target cells by increasing permeability of cell membrane</td>
</tr>
</tbody>
</table>
Mediator Systems

iii) Platelet activating factor, PAF

– PAF is derived from membrane phospholipids by the action of phospholipase A$_2$
– Generated by mast cells, platelets, endothelial cells and leukocytes
– Causes vasodilation and increases vascular permeability
– Enhances arachidonic acid metabolism in leukocytes leading to increased motility, degranulation, and free radical formation
Mediator Systems

iv) Cytokines and Chemokines

- Protein cell products that act as a message to other cells, telling them how to behave.
- Released by many cell types
- IL-1 and TNF activate endothelium and cause fever and lethargy
- IFN-γ activates macrophages/neutrophils, boosting their killing ability
- IL-8 (chemokine) is chemotactic for neutrophils
- IL-6, IL-8, TNF, IL-1 increase acute phase protein production (e.g., C-reactive protein and mannan binding lectin are opsonins that activate complement)
Mediator Systems

v) Phagocyte Products
- Leak from PMNs and macrophages after demise, attempts at phagocytosis, etc.
- Acid proteases (normally within lysosomes)
- Neutral proteases such as elastase and collagenase are destructive in ECM
- Counteracted by serum and ECM anti-proteases
Mediator Systems

vi) Nitric Oxide (NO)

- Short-acting soluble free-radical gas with many functions and is produced by endothelial cells, neurons and macrophages
- Endothelial NO synthase (eNOS) is induced by thrombin, adenoseine diphosphate (ADP) & bradykinin
- L-Arginine is metabolized in endothelial cells via eNOS to NO
- NO acts downstream to reduce platelet adhesion, decrease leukocyte adhesion, inhibit smooth muscle proliferation and migration, and induce vasodilation
- NO kills microbes in activated macrophages
Mediator Systems

vii) Arachidonic Acid (ARA)
- Mediators are known as eicosanoids
- Many cells produce eicosanoids….which ones depends on the particular cell type

acts on thermoregulatory center of hypothalamus to produce fever
Inflammation and Healing
Specialized Pro-Resolving Mediators

**SPM General Actions**
- Stop PMN transmigration and chemotaxis, brake eosinophils
- Block prostaglandins and leukotrienes
- Reduce cytokine release and function (TNFα)
- Non-phlogistic monocyte recruitment
- Uptake and removal of apoptotic PMN and microbial particles by macrophages
- Enhance anti-microbial defense mechanisms and clearance at mucosal surfaces

**Precursors**
- Arachidonic Acid (AA)
- Eicosapentaenoic Acid (EPA)
- Docosahexaenoic Acid (DHA)

**Families**
- Lipoxins
- E-Series Resolvins
- D-Series Resolvins
- Protectins/Neuroprotectins

**SPM Specific Actions**
- LXA₄
  - PMN-mediated tissue damage
  - Angiogenesis and cell proliferation
  - IR Injury
  - ROS extracellular release
  - Adhesion
  - Pro-inflammatory cytokines (TNFα, IL-12)
  - DC-lymphocyte interactions (immune synapse)
  - Phagocytosis and IL-10 production
- RvE1
  - DC IL-12 production
  - DC migration
  - Phosphorylation signals
  - Inhibit NF-κB reporter gene activation
  - Block PMN chemotaxis
  - Mucosal clearance of PMN by CD55
  - PMN detachment
  - LXA₄ production
  - ROS intracellular
  - Microbial cell cytokine expression
- RvD₁
  - Adhesion receptors
  - ROS generation & Pro-Inflammatory cytokines (TNFα, IL-8)
  - PMN transmigration
  - PGE₂ production
  - Neovascularization
  - Microbial cell cytokine expression
- RvD₂
  - PMN adhesion to endothelial cells
  - Nitric oxide and prostacyclin
  - T-cell migration
  - NF-κB and COX-2 expression
  - Renal fibrosis
  - TLR-mediated M₂ activation
  - Nitro and IFNγ release
  - Protection of retinal pigment epithelial cells
  - Neuroprotective actions
  - CCR5 expression on T-cells

**Class switching**
- Initiation
- Prostaglandins
- Leukotrienes
- Lipoxins
- Resolvins and protectins

**Time**
- Resolution
Omega-6 and Omega-3 fatty acids
Mediator Systems

• Western diet is high in omega-6 fatty acids (e.g., arachidonic acid) displacing omega-3 fatty acids (e.g., DHA and EPA) in cell membranes.

• Omega-6 derived lipid mediators (e.g., PGE2 and LTB4) may prolong inflammation and injury.

• With omega-3 supplementation, the balance of lipid mediator metabolic precursors can be restored or reversed by providing substrates for SPM production.
2d) Possible outcomes of acute inflammation

- Complete resolution
- Scarring (fibrosis)
- Abscess formation
- Progression to chronic inflammation
**INJURY**
- Infarction
- Bacterial infections
- Toxins
- Trauma

**ACUTE INFLAMMATION**
- Vascular changes
- Neutrophil recruitment
- Mediators

**CHRONIC INFLAMMATION**
- Angiogenesis
- Mononuclear cell infiltrate
- Fibrosis (scar)

**RESOLUTION**
- Clearance of injurious stimuli
- Clearance of mediators and acute inflammatory cells
- Replacement of injured cells
- Normal function

**FIBROSIS**
- Loss of function

Pus formation (abscess)
Healing
Healing
Healing

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3. Chronic inflammation
• Chronic inflammation is a prolonged process (weeks-months-years) in which three processes are occurring simultaneously:

1) Active inflammation
   • Lymphocyte, macrophage, plasma cell (mononuclear cell) infiltration

2) Tissue destruction by inflammatory cells

3) Tissue healing (repair & fibrosis)
   • 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)
3a) Chronic Inflammatory Cells

- Macrophages
  - Scattered throughout the body (microglia, Kupffer cells, sinus histiocytes, alveolar macrophages, etc.)
  - Circulate as monocytes and reach site of injury within 24 – 48 hrs and transform into macrophages
  - Become activated by T cell-derived cytokines, endotoxins, and other products of inflammation
3a) cont’d

- **T and B lymphocytes**
  - Antigen-activated (delivered via macrophages and dendritic cells)
  - Release macrophage-activating cytokines (in turn, macrophages release lymphocyte-activating cytokines until inflammatory stimulus is removed)

- **Plasma cells**
  - Terminally differentiated B cells
  - Produce antibodies
3a) cont’d

• Eosinophils
  – Found especially at sites of parasitic infection, or at allergic (IgE-mediated) sites
3b) Granulomatous Inflammation

- A special case of chronic inflammation characterized by granulomas
- Typically not preceded by an acute, PMN-mediated inflammation
- Granuloma is an organized collection of macrophages. It is a circumscribed lesion, often nodular and surrounded by collagen fibers; it is not a tumor in spite of the suffix “-oma”
3b) Granulomatous Inflammation

- Clusters of T cell-activated macrophages, which engulf and surround indigestible organisms and foreign bodies (Mycobacterium tuberculosis, Histoplasma capsulatum, silica, suture material)
3b) Granulomatous Inflammation

- Macrophages can fuse to form giant cells. **Langhans giant cells** in tuberculosis in response to indigestable micro-organisms, and **Foreign body giant cells** in response to foreign material.
4. Patterns of Acute and Chronic Inflammation

- **Serous**
  - Watery, protein-poor effusion (e.g., blister (burn), excess alveolar fluid (pneumonia))

- **Fibrinous**
  - Fibrin accumulation
  - Indicative of severe inflammation
  - Seen in many bacterial infections ("strep throat", bacterial pneumonia or bacterial pericarditis)
Patterns (cont’d)

- Purulent
  - Pus forming bacteria (streptococci and staphylococci)
  - Pus is rich in dead and dying neutrophils
  - Rich in lytic enzymes and fibrin
  - A localized collection of pus = Abscess; may be encapsulated
  - Large abscesses often drain through a fistula (tube) leaving behind a sinus or cavity
  - Fistulas can also form during inflammation between two hollow organs or between a hollow organ and the skin

Figure 2-14
Diagram of an abscess, sinus, and fistula. A. An abscess is a localized, purulent inflammation. Older abscesses are surrounded by a capsule that consists of granulation tissue. B. A sinus forms a tract connecting the abscess with the skin. This allows the drainage of pus outside the body. C. A fistula is an inflammatory tract that connects either two hollow organs or a hollow organ with the skin.
Patterns (cont’d)

• Ulcerative
  – Necrotic and eroded epithelial surface (peptic ulcer)
  – Commonly affects stomach or intestines
  – Defined as a defect in the epithelium but may extend into deeper connective tissue

• Pseudomembranous
  – Particular form of ulcerative inflammation combined with fibrino-purulent exudation
  – For example, *Clostridium difficile* causes pseudomembranous colitis
  – Fibrin, pus, cellular debris, mucus form pseudomembrane over an ulcer
  – Pseudomembrane can be scraped away to expose ulcerated defect
5. Clinical Picture

• Fever
  – IL-1 and TNF are endogenous pyrogens whose effects on the thermoregulatory centers in the hypothalamus are mediated by prostaglandins
  – Recall……Prostaglandin synthesis is blocked by NSAIDS (e.g., aspirin) which inhibit cyclooxygenase
  – Other *acute-phase reactions* include:
    • Anorexia (fever leads to loss of appetite and decreased food consumption) and skeletal muscle protein degradation
    • Hypotension and sleepiness (late fever phase)
Clinical Picture (cont’d)

• Leukocytosis
  – Elevated white blood cell count
    • Normal=4000-10,000 cells/ul
    • Leukocytosis=15,000-20,000 cells/ul
  – Bacterial infection (neutrophilia)
  – Parasitic infection (eosinophilia)
  – Viral infection (lymphocytosis)
Clinical Picture (cont’d)

- Increased erythrocyte sedimentation rate
  - Test is performed with anticoagulated blood placed in an upright tube
  - Sedimentation rate is reported in mm/h
  - During inflammation, fibrinogen content is high in plasma and causes RBCs to stick to each other ("rouleaux") and sediment faster

Time 0

(18 mm/h)

Time 60 min
6. Tissue injury and Repair

• After injury tissues may regenerate or heal.

• **Regeneration** involves restitution of tissue identical to that lost by injury. **Healing** is a fibroproliferative response that “patches” a tissue defect by laying down connective tissue; fibrosis and scar formation.
The sequence of **healing**:

1. An inflammatory response to eliminate the initial stimulus and initiate ECM deposition.
2. Proliferation & migration of parenchymal and connective tissue cells.
3. Formation of **granulation tissue**
5. Tissue remodeling
6. Wound contraction and development of wound strength.
6a) Granulation Tissue

- Repair begins early in inflammation, within 24 hours fibroblasts and vascular endothelial cells begin to proliferate to form granulation tissue (it appears pink, soft and granular).
- Microscopically granulation tissue consists of proliferating fibroblasts and new blood vessels in a loose matrix.
- The ECM is edematous because new vessels are “leaky” allowing protein and even RBC passage.
• 1-3 days after injury, macrophages, myofibroblasts and new blood vessels appear (angiogenesis)

• 3-5 days after injury, fibroblasts proliferate and secrete Collagen III

• 1-2 weeks after injury, newly formed blood vessels regress and tissue appears less red (blanched)

• Weeks to months after injury, fibroblasts secrete enzymes to breakdown Collagen III and then they secrete Collagen I in its place

• Eventually, repaired area will have 70-80% of its initial strength

**Figure 2-21**
Diagram of the histologic appearance of granulation tissue. *A*, In the early stages, it contains numerous macrophages, myofibroblasts, and blood vessels. *B*, In the late stages, the granulation tissue is less vascular. Moreover, it contains more matrix and fibroblasts and only scattered macrophages.
Cell Proliferation and Repair

• Continuously dividing/mitotic cells (labile cells)
  – Divide throughout their lifespan (e.g., stem cells found in basal layer of skin, mucosa of internal organs and limbus surrounding the cornea)
  – Cell division occurs at a regular rate and differentiated daughter cells replace shed superficial cells

• Quiescent, facultative mitotic cells (stable cells)
  – Don’t normally divide, but can be stimulated to divide
  – Example: Liver regeneration after partial hepatectomy

• Nondividing, postmitotic cells (permanent cells)
  – Never divide (e.g., neurons, myocardial cells)
  – Following injury, repair is by fibrous scarring
Repair by Regeneration or Scar Formation?

- **Regeneration**
  - Labile (stem) cells and quiescent (stable) cells
  - If injury was small and of short duration, cells can regenerate damaged tissue

- **Scar Formation**
  - Postmitotic (permanent) cells
  - If the injury was large and cells cannot grow

* Often repair involves both regeneration and scar formation processes
6b) Clinical Wound Healing

• First Intention/Primary Healing

• Second Intention/Secondary Healing
First Intention/Primary Healing

- When wound edges are directly next to one another
- Little tissue loss
- Minimal scarring occurs
- Most surgical wounds heal by first intention healing
- Wound closure is performed with sutures, staples, or adhesive at the time of initial evaluation
Second Intention/Secondary Healing

- Healing of large wounds where edges cannot be drawn together
- Wound care must be performed daily to encourage wound debris removal and allow for granulation tissue formation
- Myofibroblasts help bring the edges together
- Granulation results in a broad scar