Inflammation and Repair (Fall 2017)

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Outline – 2 Lectures

1) Inflammation
   a) Define

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) Repair by healing, scar formation and fibrosis
   a) Granulation tissue
   b) Clinical wound healing
1. Inflammation

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

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

a) Vascular
   • Vasodilation and Vascular leakage (edema)

b) 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
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 basement membrane 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**)
- Blood viscosity ↑ and leukocytes marginate (**pavementing**) along the vessel wall
2b) Cellular events

- **Diapedesis:**
  - Leukocytes leave the vasculature and enter the interstitium through the following sequence of events:
    - Margination, tethering and rolling
    - Firm adhesion and transmigration
    - Chemotaxis and activation

- **Extravascular Leukocytes engage 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
    • Pro-inflammatory (M1)
    • Anti-inflammatory (M2)
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)
    • Eosinophil peroxidase and major basic protein can contribute to local pathology (asthma and inflammatory bowel disease)
    • Evolved to attack IgE- and C3b-coated parasites (e.g., helminths like schistosomula)
Schistosomula life-cycle
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 contact with 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 were described in “great” detail by Dr. Redfern
Leukocyte Recruitment at Inflammatory Sites
Neutrophil Recruitment on IL-1-activated human endothelium
Chemotaxis

- Leukocytes follow chemical gradient to site of injury (chemotaxis)
  - Soluble bacterial products
  - Complement components (C5a)
  - Chemokines (e.g., IL-8)
  - LTB₄ (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
Oxygen-dependent killing

- 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

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

- Granule contents:
  - Bactericidal permeability increasing protein (BPI)
  - Lysozyme
  - Lactoferrin
  - Defensins (punch holes in membranes)

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

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

- C-reactive protein (first described as a substance reacting with a Pneumococcal carbohydrate antigen ........making it the first pattern recognition receptor)
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 (coagulation) factors
• Complement cascade
Clotting (coagulation)

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

Contact Activation Pathway

INTRINSIC PATHWAY

Collagen or other activators

Active XII

Ca²⁺

Active XI

IX

Ca²⁺

Active IX

VII

Damage exposes tissue factor (III)

tissue factor (III) and active VII

positive feedback

Ca²⁺

phospholipids (PL)

COMMON PATHWAY

positive feedback

Active X

Prothrombin

Ca²⁺, V, PL

Thrombin

Fibrinogen

XIII

Active XIII

Ca²⁺

Cross-linked fibrin

EXTRINSIC PATHWAY

Tissue Factor Pathway
Dissolving the Clot

- Bleeding stopped
- Vessel repair
- Plasmin
- Fibrinolysis
- Clot dissolved
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
Classical Complement Pathway triggered by C-reactive protein* or antibodies bound to foreign cells

* An acute phase protein secreted into blood by the liver

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 is 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
Classical and Alternative Complement Pathways trigger C3 cleavage. C3 is the most pivotal and abundant complement component.
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.
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.
A third pathway is the Lectin Pathway
## 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) Arachidonic Acid mediators (eicosanoids)
- Many cells produce eicosanoids…which ones depends on the particular cell type

![Diagram showing the pathway of eicosanoids formation](image-url)
iv) Platelet activating factor, PAF
- Like the eicosanoids, 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
v) 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; C-reactive protein (opsonin) and mannan binding lectin (opsonin) activate complement
vi) 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
vii) 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, adenosine 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
2d) Possible outcomes of acute inflammation

- Complete resolution
- Scarring (fibrosis)
- Abscess formation
- Progression to chronic inflammation
ACUTE INFLAMMATION
- Vascular changes
- Neutrophil recruitment
- Mediators

INJURY
- Infarction
- Bacterial infections
- Toxins
- Trauma

Progression

Healing

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

Pus formation (abscess)

Healing

INJURY
- Viral infections
- Chronic infections
- Persistent injury
- Autoimmune diseases

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

FIBROSIS
- Loss of function
Resolution of inflammation; note the major role of macrophages.
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
  - PMN chemotaxis
  - Angiogenesis and cell proliferation
  - 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 killing

- RvE1
  - Adhesion receptors
  - ROS generation & pro-inflammatory cytokines (TNFα, IL-8)
  - PMN transmigration
  - LXA4 production
  - ROS intracellular
  - Microbial cell cytokine expression

- RvD1
  - PMN adhesion to endothelial cells
  - Nitric oxide and prostacyclin in endothelial cells
  - Microvascularity
  - Microbial killing and clearance

- RvD2
  - NFκB and COX-2 expression
  - Renal fibrosis
  - TLR-mediated Mφ activation
  - TNF 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  Resolution

Time
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, endotoxin, and mediators 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)

- 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.

- Surrounding the giant cells are squamous epithelioid cells derived from macrophages, along with lymphocytes, plasma cells, fibroblasts and collagen

- Caseous (cheese-like) necrosis is common with infectious causes (e.g., bacterial tuberculosis)
Foreign body (arrow)
Giant Cell

Langhans giant cells
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)

*Figure 2-11*
Fibrinous pericarditis. The epicardium is covered with a shaggy layer of fibrin.
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
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

Time 60 min
(18 mm/h)
6. Repair by Healing, Scar Formation and Fibrosis

1. After injury tissues may regenerate or heal.
2. **Regeneration** involves restitution of tissue identical to that lost by injury, **healing** is a fibroproliferative response that “patches” a tissue defect.
3. Some tissues are capable of **healing** (bone after a fracture, epithelium after a superficial wound), for most tissues repair is accomplished by ECM deposition resulting in a **scar**.
4. In chronic inflammation both tissue injury and repair involve ECM deposition as **fibrosis** (an abnormal deposition of connective tissue).
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.
1-3 days after injury, macrophages, myofibroblasts and new blood vessels appear (angiogenesis) – **tissue appears pink, soft and granular**

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
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, of short duration and if cells can regrow

• Scar Formation
  – Postmitotic (permanent) cells
  – If the injury was large and cells cannot grow

* Often repair involves both regeneration and scar formation
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 and minimal scarring
- 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 performed daily to encourage debris removal and allow for granulation tissue formation

- Myofibroblasts help bring the edges together

- Granulation results in a broad scar