

## Chapter 9 Inflammation and Dysfunctional Wound Healing

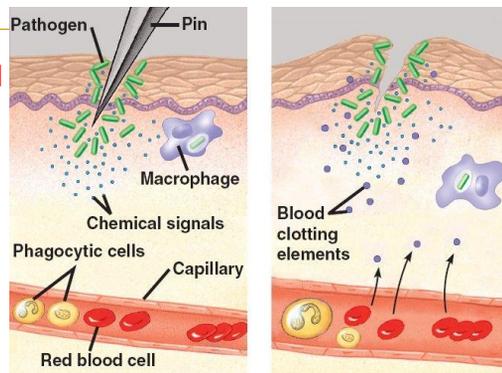
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### Inflammation Overview

- **Inflammation is a coordinated to any injury**
- **Goal** → *to protect and restore*
  - Wall off injured area
  - Prevent spread of injury
  - Bring body's defenses to needed area
- **It is a multi-stage process**
  - *Involves VASCULAR and CELULAR changes*
  - Local or systemic
  - Acute or chronic



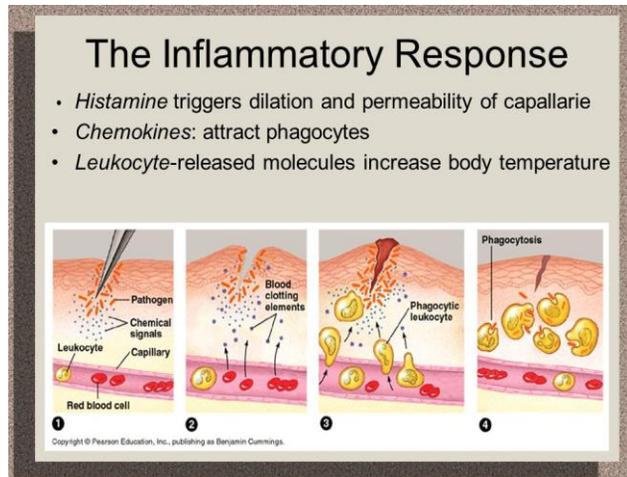
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## Acute Inflammation

- Rapid onset
  - Terminates quickly
  - Chemical mediators orchestrate response
- 
- 3 phases
    1. Increased vascular permeability
    2. Cellular chemotaxis
    3. Systemic response



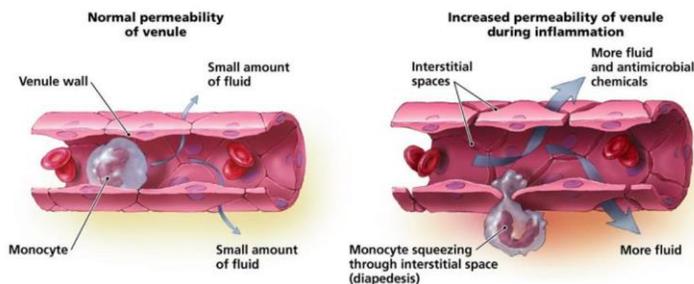
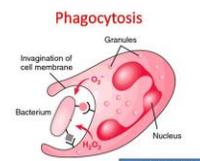
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### 1. Increased Vascular Permeability

- Histamine and bradykinin: dilate vessels
- Fluid, WBCs, platelet travel to injury
- Toxins diluted
- WBCs phagocytize foreign matter and debris



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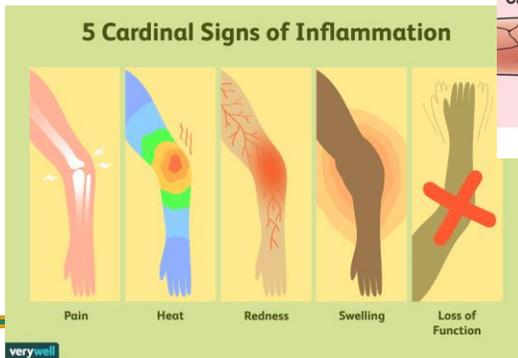
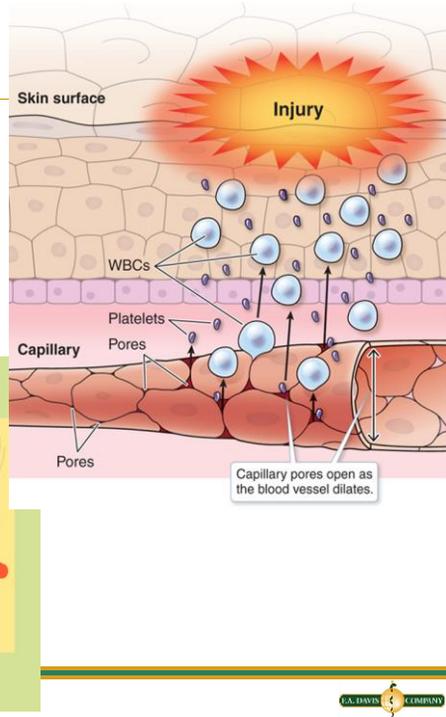


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# Vascular Permeability

## 5 Classic signs of inflammation

1. Rubor (redness)
2. Tumor (swelling)
3. Calor (heat)
4. Dolor (pain)
5. Loss of function (function laesa)



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# Vascular Permeability (continued\_2)

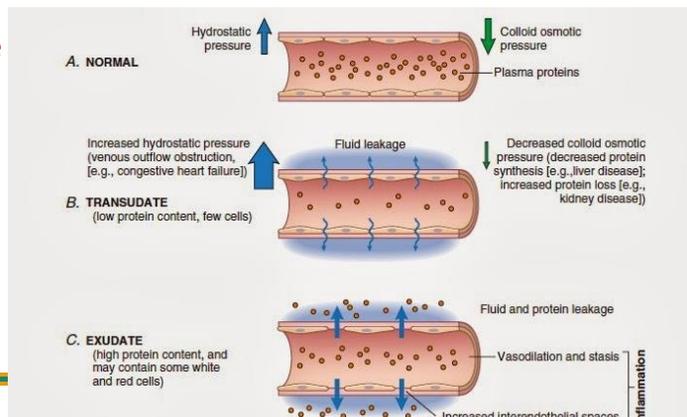
■ *Vasodilation and fluid extravasation into the tissues*

■ **Transudate**

- Watery, clear fluid
- *Example:* non-infected blister

■ **Purulent exudate (pus)**

- Proteins, microbes, cell debris
- White-green discharge



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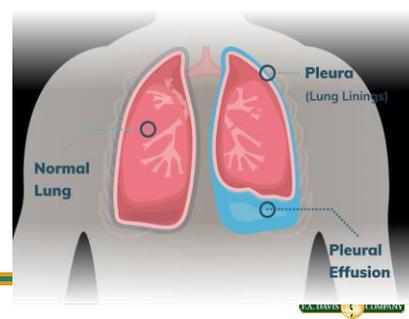
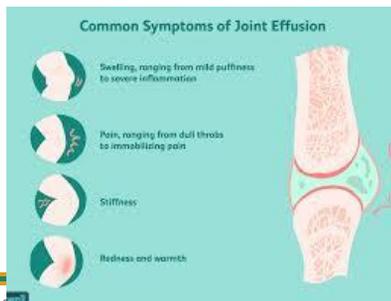
## Vascular Permeability (continued\_3)

### ■ Abscess

- Localized, walled-off collection of purulent exudate

### ■ Effusion

- Accumulation of fluid in a body cavity



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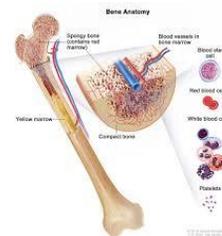
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## Cellular Chemotaxis

- *Chemical signals from WBCs, endothelial cells, microbial agents → attract WBCs and platelets*

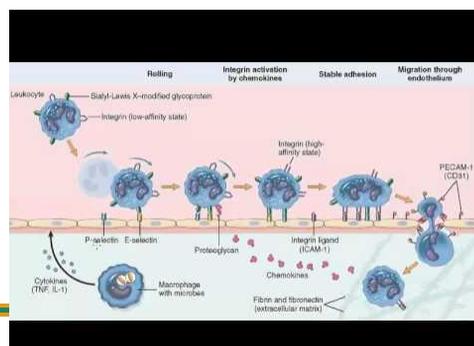
- During this phase:

- Bone marrow releases an increased number of leukocytes (WBCs)
- WBC count in the blood commonly increases from a normal baseline (4,000 – 10,000 cells/ml) to 15,000-20,000 cells/ml.



- Margination

- WBCs line up along endothelium
- Release inflammatory mediators

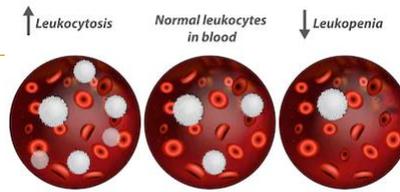


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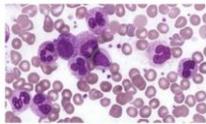
## White Blood Cells

- **Leukocytosis**
  - Increase in WBC number
- **Leukemoid reactions**
  - Extreme elevation in WBC
- **WBC Differential**
  - Different types of WBCs



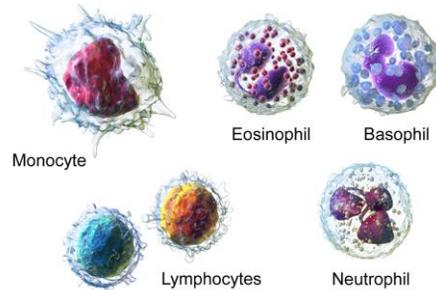
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### Leukemoid Reaction



Marked increase in neutrophils.  $>50,000 \times 10^9$   
 Shift to left  $\rightarrow$  Immature forms.  
 Severe infection, trauma, bone marrow infiltration  
 Looks like leukemia\*  
 (no blasts)

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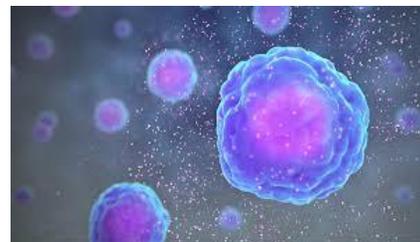
### White Blood Cells

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## Inflammatory Mediators

- Promote/inhibit inflammation
- Many pharmacological agents modulate
- **Cytokines**
  - Released by WBCs
  - Tumor Necrosis Factor (TNF) alpha
  - Interleukins (ILs)
- **Chemokines**
  - Proteins that attract leukocytes to the endothelium



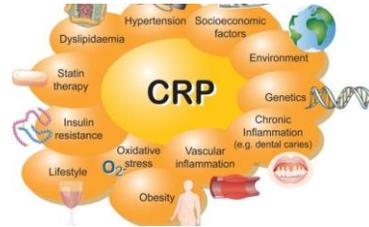
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## Acute Phase Proteins

- Cytokines stimulate the liver to produce and release:
- C-reactive protein (CRP)
  - Marks foreign material for phagocytosis
  - Activates complement system
  - Stimulates other inflammatory cytokines
  - **Elevation indicates active inflammation**
- **High sensitivity CRP**: elevation of this protein is a marker for increased risk of myocardial infarction in patients with coronary artery disease.



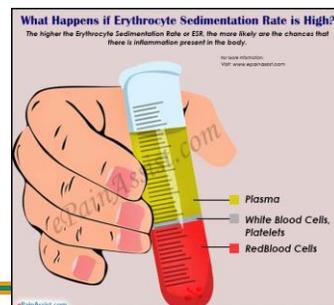
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## Acute Phase Proteins (continued\_1)

- Fibrinogen
  - Binds to red blood cells and fixes them into stacks that precipitate
    - Processes called rouleaux and sedimentation
    - Lab test Erythrocyte sedimentation rate (ESR)
      - If elevated = Active inflammation



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## Acute Phase Proteins (continued\_2)

- Serum amyloid A
  - Amyloidosis
    - Prolonged secretion which indicates chronic inflammation
- Hepcidin
  - Elevation indicates diminished iron storage in the body
  - Anemia with chronic inflammation

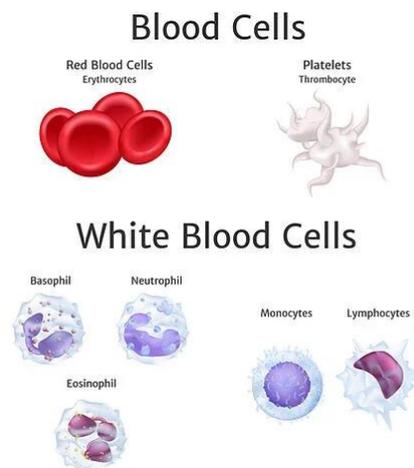
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## White Blood Cells (continued\_1)

- Different types of WBCs
  - Granulocytes
    - Neutrophils
    - Basophils
    - Eosinophils
  - Agranulocytes
    - Monocytes
    - Lymphocytes

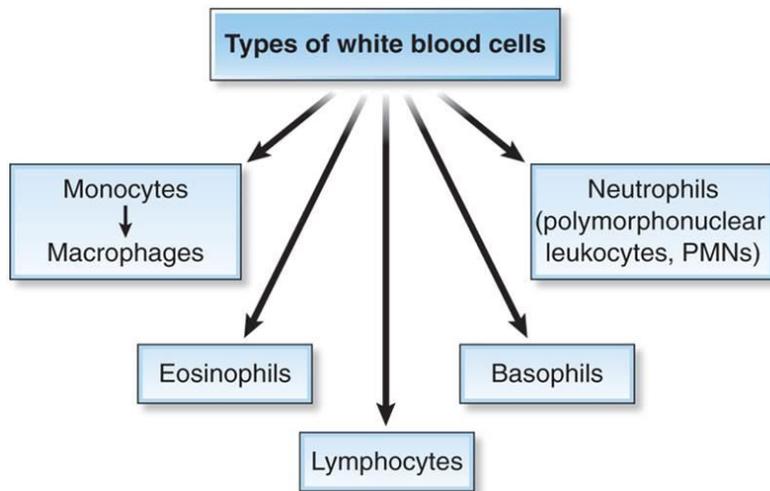


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## White Blood Cells (continued\_2)



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## White Blood Cell Response

- 1st 6–24 hours
  - Neutrophils
    - Neutrophils gradually replaced by monocytes
- 24–48 hours
  - Monocytes to macrophages
    - Macrophages predominate in persistent inflammation
    - Macrophages carry out phagocytosis
- Viral infections
  - Lymphocytes dominate

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## Neutrophils

- Short lifespan: hours to days
- Acute responder
- Phagocytosis
  - Respiratory burst releases free radicals that destroy microbes
- Also known as PMNs (polymorphonuclear cells)
  - Mature neutrophils: segmented nuclei
  - Immature neutrophils: known as “bands”
    - Acute infection results in “shift to left” as more “bands” are produced than “segs”

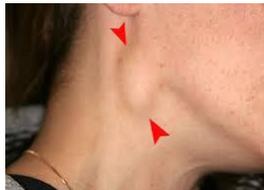
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## Systemic Responses in Acute Inflammation

- **Fever**
  - **Lymphadenopathy**
  - **Anorexia**
  - **Sleepiness**
  - **Lethargy**
  - **Anemia**
  - **Weight loss**
- Most signs due to chemical mediators:
    - Pyrogens, TNF-alpha, interleukins
  - Drugs to reduce inflammation target these signals

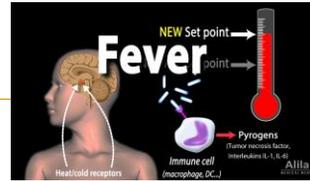


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## Fever



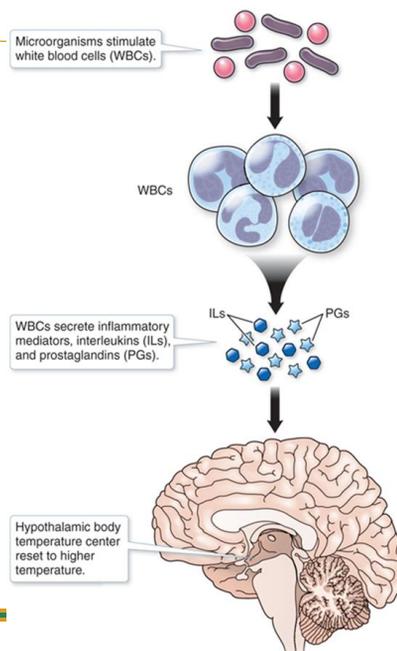
- **Pyrogens cause fevers**
  - WBCs and microorganisms release **signals** causing prostaglandins to reset temperature
  - **Higher temperatures increase WBC efficiency**
  - Anti-prostaglandins reduce fever
  - **Reye's syndrome**
    - **Never give children or adolescents aspirin to reduce fever**
- Fever onset
  - **Shivering** to increase temperature
- Fever “breaks”
  - **Sweating** to reduce temperature

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## Fever (continued)

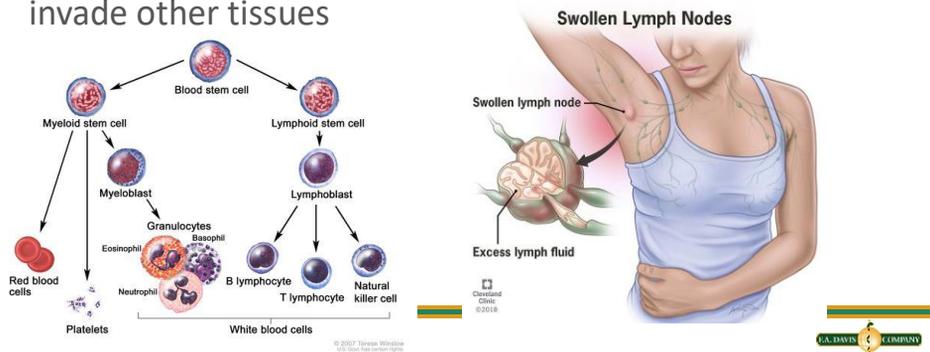


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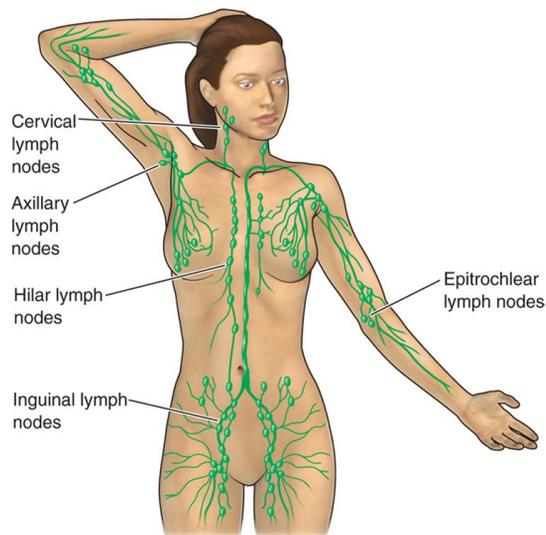
## Lymphadenopathy

- Enlargement of lymph nodes, often due to inflammatory process
- Lymphocytes (B and T cells) mature in lymph nodes
- Lymphatic fluid circulates throughout the body, thus injurious agents in the lymph system can invade other tissues



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## Lymphatic System



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## Histamine

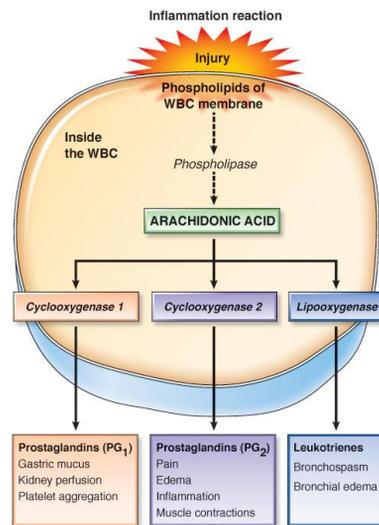
- Produced by basophils, platelets, and mast cells
- Systemic effects
  - Arteriolar vasodilation
  - Large artery vasoconstriction
  - Increased permeability of venules
- *Example: sneezing, runny nose, pharyngeal irritation in upper respiratory tract*



## Prostaglandins and Leukotrienes

- Phospholipase breaks down phospholipids to form arachidonic acid (AA)
- AA converted to PGs and leukotrienes
  - Cyclooxygenase-1 (cox-1)
    - Helpful PGs; mucus production to protect gastric mucosa
  - Cyclooxygenase-2 (cox-2)
    - Inflammatory PGs; cause pain, fever, swelling
  - Lipoxygenase
    - Forms leukotrienes
    - Bronchiole contraction in asthma

## Prostaglandins and Leukotrienes (continued)



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## TNF-alpha and Interleukins

- TNF-alpha and ILs
  - **Inflammatory signals** produced by macrophages
  - Induce **fever**, **loss of appetite**, and **lethargy**
  - TNF-alpha promotes **weight loss** and **cachexia**
  - TNF-alpha **increases endogenous corticosteroids**

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## Outcomes of Acute Inflammation

- Complete resolution 
- Healing by connective tissue
  - Regeneration of normal cells does not occur
  - Excessive proliferation of connective tissue, fibrous scar tissue formed 
- Chronic, persistent inflammation 
  - Resolution does not occur
  - Extensive tissue damage may occur

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## Chronic Inflammation

- Inflammation for weeks or months with no resolution or healing
- Persistent infection
  - Tuberculosis, syphilis, viruses
- Hypersensitivity disorders
  - Rheumatoid arthritis, Systemic Lupus Erythematosus (SLE)
- Exposure toxic agents
  - Coal dust—Anthracosis (Black Lung)
- Atherosclerosis
  - Chronic inflammatory disease

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## Chronic Inflammation Differs From Acute

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- Predominance of monocytes, lymphocytes, and macrophages
- **Continual secretion of cytokines damages healthy tissues stimulating further inflammation**
- **Granuloma formation**
  - Macrophages aggregate and are transformed into epithelial-like cells
- T and B lymphocytes amplify and perpetuate inflammatory signals
  - Autoimmune disorders

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## Tuberculosis and Granuloma Formation

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## Wound Healing

- Four Phases
  1. Hemostasis
  2. Inflammation (described previously)
  3. Proliferation, granulation tissue formation, angiogenesis, epithelialization
  4. Wound contraction and remodeling

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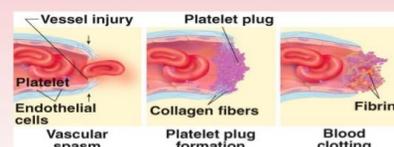
## Hemostasis

- Exposed collagen of injury attracts platelets
- Platelets aggregate and secrete inflammatory mediators
- Vasoactive amines cause short-term vasoconstriction

### STAGES OF HEMOSTASIS:

When a blood vessel is injured, the injury initiates a series of reactions, resulting in hemostasis. It occurs in three stages.

1. Vasoconstriction.
2. Platelet plug formation.
3. Coagulation of blood.



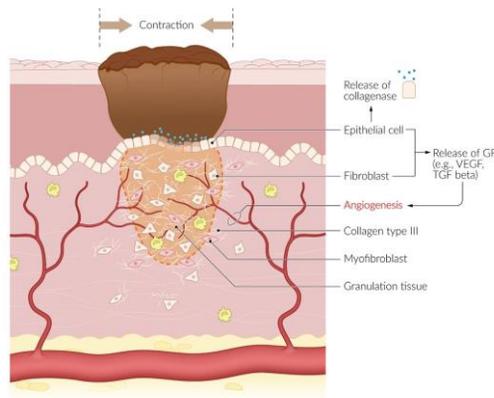
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## Proliferation and Granulation

- Fibroblasts
  - Connective tissue cells
  - Synthesize collagen
  - Create foundation of scar tissue
- Angiogenesis
  - VEGF from vascular endothelial cells
- Epithelial cells
  - Migrate and proliferate to fill in the wound gap
- Approximately 3 weeks after injury, remodeling begins
  - Scar tissue refined and reshaped



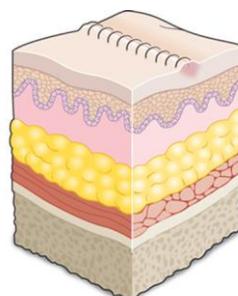
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## Primary Intention

- Clear wound edges (think surgical incision)
- No missing tissue
- Simple epithelialization
- By day 5, granulation tissue
- By the end of the first month, connective tissue covered by an intact epidermis



### Primary intention

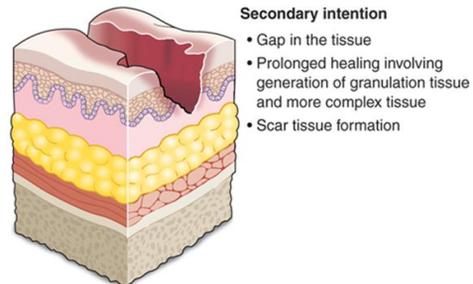
- No gap in the tissue
- Simple reapproximation of edges of wound
- Simple reepithelialization
- Surgical incision type of healing

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## Secondary Intention

- Extensive tissue loss
  - Regeneration with same cell type is not possible
- Granulation and fibrotic tissue formation
- Longer healing time with wound contraction to close gap
  - Myofibroblasts
  - Scarring



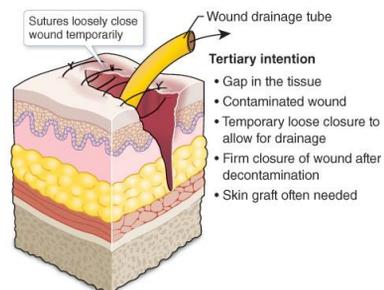
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## Tertiary Intention

- **Missing large amount of deep tissue**
  - Cleaned and left open
  - Temporary packing with sterile gauze
  - Prominent scarring, skin graft often required



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## Tertiary Intention (continued)

- Pressure ulcers and severe burns
- Primary, secondary, and tertiary intention wounds do not regain full tensile strength
  - Clinicians should be aware of skin fragility

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## Eschar and Debridement

- Eschar
  - Dead tissue that sheds or falls off from healthy skin
  - Tan, brown, or black with crusty top
- Debridement
  - Removal of necrotic tissue
  - Promotes re-epithelialization



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## Factors That Affect Wound Healing

- **Nutrition**
  - Positive nitrogen balance
- **Blood flow and oxygen delivery**
- **Immune strength**
- **Infection**
  - Single most significant factor in delayed wound healing
- **Foreign bodies**
- **Mechanical factors**

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## Dysfunctional Wound Healing

- **Wound Rupture**
  - **High tension**
    - *Example:* Abdominal wall and coughing
  - **Wound dehiscence**
    - Previously closed wound edges open and rupture
  - **Wound evisceration**
    - Internal tissues and organs protruding from open wound
  - **Require protection with sterile, saline-moistened dressings**



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FIGURE 1

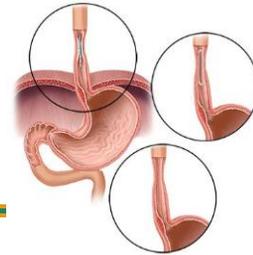


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## Dysfunctional Wound Healing (continued\_1)

- **Keloid formation**
  - Hyperplastic epithelialization leading to hypertrophic scar
- **Contractures**
  - Inflexible shrinkage of a wound
  - Can limit mobility
- **Stricture**
  - Narrowing of an open area
  - *Example: esophagus*

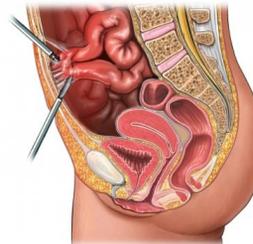
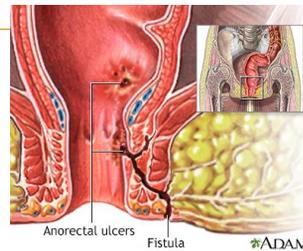


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## Dysfunctional Wound Healing (continued\_2)

- **Fistula**
  - Abnormal connection between two structures
  - *Example:* tracheoesophageal fistula
- **Adhesion**
  - Abnormal bands of internal scar tissue that can limit mobility



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