Lec 7

# General pathology

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## Wound healing

**Wound healing refers to a living organism's replacement of destroyed or damaged tissue by newly produced tissue.**

**his process is divided into predictable phases:**

1. **blood clotting (hemostasis).**
2. **inflammation.**
3. **tissue growth (cell proliferation).**
4. **tissue remodeling (maturation and cell differentiation).**

## Types of Wound healing:

1. **Healing by First Intention (primary union).**
2. **Healing by Second Intention (secondary union).**

## Healing by First Intention:

1. **When the injury involves only the epithelial layer, the principal mechanism of repair is epithelial regeneration.**
2. **healing of a clean, uninfected surgical incision approximated by surgical sutures.**
3. **The incision causes only focal disruption of epithelial basement membrane continuity.**
4. **death of relatively few epithelial and connective tissue cells.**

5. **Healing by inflammation, proliferation of epithelial and other cells, and maturation of the connective tissue scar.**

## ***Mechanism of primary union*:**

1. **Wounding causes the rapid activation of coagulation pathways, which results in the formation of a blood clot on the wound surface.**
2. **Within 24 hours, neutrophils are seen at the incision margin, migrating toward the fibrin clot.**
3. **Basal cells at the edge of the incision begin to show increased mitotic activity.**
4. **Within 24 to 48 hours, epithelial cells from both edges have begun to migrate and proliferate yielding a thin but continuous epithelial layer that closes the wound.**
5. **By day 3, neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space.**
6. **By day 5, neovascularization reaches its peak as granulation tissue fills the incisional space, Fibroblasts progressively migrate into the granulation tissue, where they proliferate and lay down collagen and ECM**
7. **During the second week, there is continued collagen accumulation and fibroblast proliferation.**
8. **By the end of the first month, the scar comprises a cellular connective tissue largely devoid of inflammatory cells and covered by an essentially normal epidermis.**

## Healing by Second Intention

**Healing by second intention, also called secondary union, differs from primary healing in several respects.**

**• In wounds causing**

**a. large tissue deficits,**

**b. the fibrin clot is larger**

**c. more exudate and necrotic debris in the wounded area.**

d. **Inflammation is more.**

e. **Much larger amounts of granulation tissue are formed to fill a bigger gap caused by the larger area of deficit. Results in a greater mass of scar tissue.**

### Mechanism of heling by secondary union

- **firstly, matrix containing fibrin, plasma fibronectin, and type III collagen is formed.**
- **in about2 weeks this is replaced by a matrix composed primarily of type I collagen.**
- **By the end of the first month, the scar is made up of acellular connective tissue devoid of inflammatory infiltrate.**
- **Wound contraction helps to close the wound by formation of a network of myofibroblasts, which are modified fibroblasts which have contractile properties.**
- **Within 6 weeks, large skin defects may be reduced to 5% to 10% of their original size, largely by contraction.**

## Differences between primary healing and secondary healing in several respects

1. **In wounds causing large tissue deficits, the fibrin clot is larger, and there is more exudate and necrotic debris**
2. **Inflammation is more intense.**
3. **Much larger amounts of granulation tissue are formed resulting in a greater mass of scar tissue.**
4. **Firstly, matrix containing fibrin, plasma fibronectin, and type III collagen is formed.**
5. **in 2 weeks this is replaced by a matrix composed primarily of type I collagen.**
6. **By the end of the first month, the scar is made up of acellular connective tissue devoid of inflammatory infiltrate.**
7. **Wound contraction involves the formation of a network of myofibroblasts, which are modified fibroblasts which have contractile properties.**

8. **Within 6 weeks, large skin defects may be reduced to 5% to 10% of their original size, largely by contraction.**

**Steps in Scar Formation**

**Repair by connective tissue deposition consists of sequential processes that follow tissue injury.**

**Follows 4 steps:**

1. **inflammation.**
2. **Cell proliferation by**
   a. **Epithelial cells respond to locally produced growth factors and migrate over the wound to cover it up.**
   b. **Endothelial cells and pericytes proliferate to form new blood vessels, a process known as *angiogenesis.***
   *c.* ***Fibroblasts*** **proliferate and migrate into the site of injury and lay down collagen fibers that form the scar.**
3. **Formation of granulation tissue by**
   a. **Migration and proliferation of fibroblasts**
   b. **deposition of loose connective tissue, together with the vessels and interspersed mononuclear leukocytes, form granulation tissue.**

**The term granulation tissue derives from the pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound.**

***Its histologic appearance*** **is characterized by proliferation of fibroblasts and new thin-walled, delicate capillaries (angiogenesis) in a loose ECM, often with admixed inflammatory cells, mainly macrophages.**

4. **Deposition of connective tissue by deposition of collagen resulting in the formation of a stable fibrous scar.**

   **The laying down of connective tissue occurs in two steps:**

   a. **migration and proliferation of fibroblasts into the site of injury.**
   b. **deposition of ECM proteins produced by these cells.**

**TGF-β is the most important cytokine for the synthesis and deposition of connective tissue**

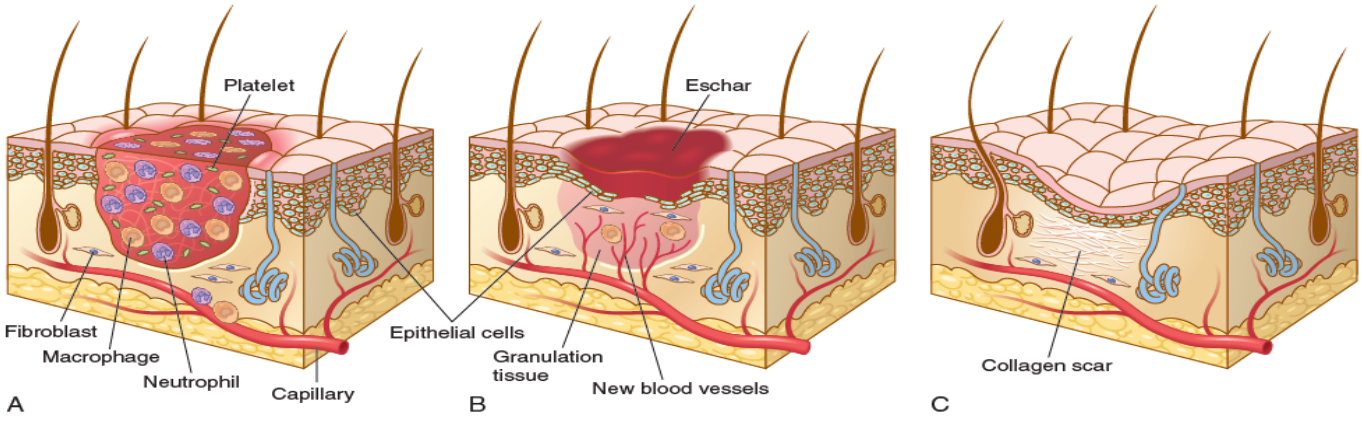


Figure 3.26 Steps in repair by scar formation: wound healing in the skin. (A) Inflammation. (B) Proliferation of epithelial cells; formation of granulation tissue by vessel growth and proliferating fibroblasts. (C) Remodeling to produce the fibrous scar.

**proteins.**

**Macrophages play a central role in repair by clearing offending agents and dead tissue, providing growth factors for the proliferation of various cells, and secreting cytokines that stimulate fibroblast proliferation and connective tissue synthesis and deposition.**

**Angiogenesis:**

**Angiogenesis is the process of new blood vessel development from existing vessels. and consists of the following steps:**

**1. Vasodilation in response to nitric oxide and increased permeability induced by vascular endothelial growth**

**factor (VEGF).**

**2. Separation of pericytes from the abluminal surface and breakdown of the basement membrane to allow formation of a vessel sprout.**

**3. Migration of endothelial cells toward the area of tissue injury.**

**4. Proliferation of endothelial cells just behind the leading front (“tip”) of migrating cells.**

**5. Remodeling into capillary tubes.**

**6. Recruitment of periendothelial cells (pericytes for small capillaries and smooth muscle cells for larger vessels) to form the mature vessel.**

**7. Suppression of endothelial proliferation and migration and deposition of the basement membrane.**

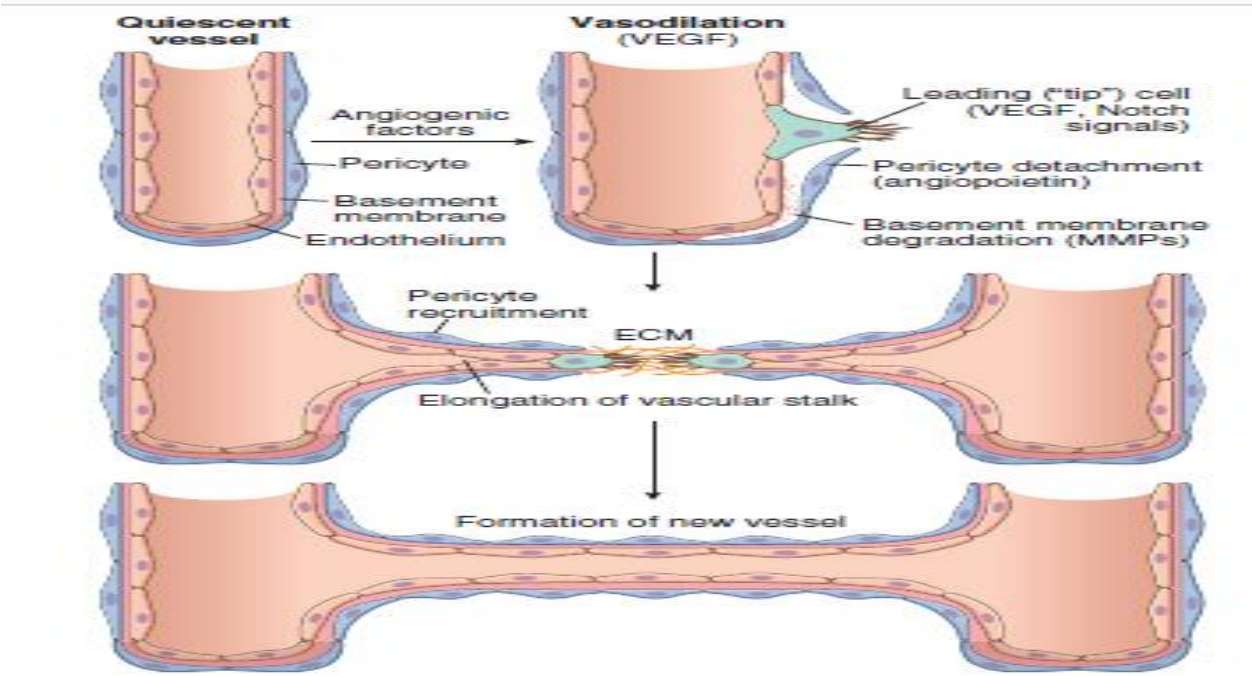


Figure 3.28 Angiogenesis. In tissue repair, angiogenesis occurs mainly by sprouting of new vessels. The steps in the process and the major signals involved are illustrated. The newly formed vessel joins up with other vessels (not shown) to form the new vascular bed. *ECM*, Extracellular matrix; *MMPs*, matrix metalloproteinases; *VEGF*, vascular endothelial growth factor.

## Remodeling of Connective Tissue

**The outcome of the repair process is influenced by a balance between synthesis and degradation of ECM proteins.**

**After its deposition, the connective tissue in the scar continues to be modified and remodeled. The degradation of collagens and other ECM components is accomplished by a family of matrix metalloproteinases (MMPs), so called because they are dependent on metal ions (e.g., zinc) for their activity. MMPs include interstitial collagenases (MMP-1, MMP-2, and MMP-3), MMPs are produced by a variety of cell types**

**1.fibroblasts,**

**2.macrophages,**

**3.neutrophils,**

**3.synovial cells, and**

**4.some epithelial cells.**

**their synthesis and secretion are regulated by growth factors, cytokines, and other agents. In addition, activated collagenases can be rapidly inhibited by specific tissue inhibitors of metalloproteinases (TIMPs), produced by most mesenchymal cells. Thus, during scar formation, MMPs are activated to remodel the deposited ECM, and then their activity is shut down by the TIMPs.**

**<u>Liver Regeneration</u>**

**The human liver has a remarkable capacity to regenerate, as demonstrated by its growth after partial hepatectomy, which may be performed for tumor resection or for living donor hepatic transplantation.**

**Regeneration of the liver occurs by two major mechanisms:**

1. **proliferation of remaining hepatocytes**
2. **repopulation from progenitor cells.**
    1. **Proliferation of hepatocytes following partial hepatectomy. In humans, resection of up to 90% of the liver can be corrected by proliferation of the residual hepatocytes. triggered by the combined actions of cytokines and polypeptide growth factors.**
    2. **Liver regeneration from progenitor cells. In situations where the proliferative capacity of hepatocytes is impaired, such as after chronic liver injury or inflammation, progenitor cells in the liver contribute to repopulation.**

**if the residual tissue is structurally intact, as after partial surgical resection→ Normal Restoration can occur.**

**if the tissue is damaged by infection or inflammation→ regeneration is incomplete and leading to scar.**

**Defects in Healing: Chronic Wounds:**

**These are seen in numerous clinical situations, as a result of local and systemic factors. The following are some common examples.**

1. **Venous leg ulcers: develop most often in elderly people as a result of chronic venous hypertension, which may be caused by severe varicose veins or congestive heart failure. Deposits of iron pigment (hemosiderin) are common, resulting from red cell breakdown, and there may be accompanying chronic inflammation. These ulcers fail to heal because of poor delivery of oxygen to the site of the ulcer.**
2. **Arterial ulcers: develop in individuals with atherosclerosis of peripheral arteries, especially associated with diabetes. The ischemia results in atrophy and then necrosis of the skin and underlying tissues. These lesions can be quite painful.**
3. **Diabetic ulcers: affect the lower extremities, particularly the feet. There is tissue necrosis and failure to heal as a result of vascular disease-causing ischemia, neuropathy, systemic metabolic abnormalities, and secondary infections. *Histologically*, these lesions are characterized by epithelial ulceration and extensive granulation tissue in the underlying dermis.**
4. **Pressure sores: are areas of skin ulceration and necrosis of underlying tissues caused by prolonged compression of tissues against a bone, e.g., in elderly patients with numerous morbidities lying in bed without moving. The lesions are caused by mechanical pressure and local ischemia.**

## Excessive Scarring:

**Excessive formation of the components of the repair process can give rise to hypertrophic scars and keloids.**

**1.The accumulation of excessive amounts of collagen may give rise to a raised scar known as a hypertrophic scar. These often grow rapidly and contain abundant myofibroblasts, but they**

**tend to regress over several months. Hypertrophic scars generally develop after thermal or traumatic injury that involves the deep layers of the dermis.**

**2. If the scar tissue grows beyond the boundaries of the original wound and does not regress, it is called a keloid. Keloid formation seems to be an individual predisposition, and for unknown reasons it is somewhat more common in African Americans.**

**3. Exuberant granulation is another deviation in wound healing consisting of the formation of excessive amounts of granulation tissue, which protrudes above the level of the surrounding skin and blocks reepithelialization. Excessive granulation must be removed by cautery or surgical excision to permit restoration of the continuity of the epithelium.**

**Contraction in the size of a wound→ normal healing process**

**Exaggeration of wound healing→ contracture→ deformities of the wound and the surrounding tissues.**

**Example of contracture:**

1. **palms**
2. **soles**
3. **anterior aspect of the thorax**
4. **serious burns and can compromise the movement of joints**

## HEALING OF BONE FRACTURES

**Fractures are defined as loss of bone integrity resulting from mechanical injury and/or diminished bone strength.**

**They are some of the most common pathologic conditions affecting bone.**

- **Simple: the overlying skin is intact.**
- **Compound: the bone communicates with the skin surface.**
- **Comminuted: the bone is fragmented.**

**• Displaced: the ends of the bone at the fracture site are not aligned.**

**• Stress: a slowly developing fracture that follows a period of increased physical activity in which the bone is subjected to repetitive loads.**

**• Greenstick: extending only partially through the bone, common in infants when bones are soft.**

**• Pathologic: involving bone weakened by an underlying disease process, such as a tumor.**

## HEALING OF FRACTURES

- **Bone has a remarkable capacity for repair. Immediately after fracture, rupture of blood vessels results in a *hematoma* that fills and surrounds the area of injury.**
- **The clot provides a *fibrin mesh that seals the fracture site* and provides a framework for the inflammatory cell influx, fibroblast ingrowth, and capillary proliferation that characterize granulation tissue.**
- **Release of PDGF, TGF-β, FGF, and other growth factors by degranulated platelets and inflammatory**

  **cells activate osteoprogenitor cells in the periosteum, medullary cavity, and surrounding soft tissues to stimulate osteoclastic and osteoblastic activity. Uncalcified tissue known as *soft tissue callus or procallus forms,* providing some anchorage but not structural rigidity for weight bearing.**
- **After approximately 2 weeks, the soft callus is *transformed into a bony callus*. The activated osteoprogenitor cells *deposit woven bone***
- **Activated soft tissue mesenchymal cells may also differentiate into chondrocytes that produce fibrocartilage and hyaline cartilage. Endochondral ossification creates a contiguous network of bone and newly deposited bone trabeculae in the medulla and beneath the periosteum. As a result, fractured bone ends are bridged and, with progressive mineralization, the stiffness and strength of the callus increases to allow weight bearing.**

- **This remodeling reduces the size of the callus until the shape and outline of the fractured bone are reestablished as *lamellar bone*. The healing process is complete with restoration of the medullary cavity.**

**<u>FACTORS BLOCKED BONE HEALING</u>:**

1. **Displaced and comminuted fractures frequently result in some deformity.**
2. **Inadequate immobilization permits movement of the callus and prevents its normal maturation, resulting in delayed union or nonunion. If a nonunion persists, the malformed callus undergoes cystic degeneration, and the luminal surface may become lined by synovial like cells, creating a false joint or pseudoarthrosis.**
3. **Infection of the fracture site, especially common in open fractures, is a serious obstacle to healing.**
4. **4. Malnutrition and skeletal dysplasia.**