Healing III
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Healing of skin wounds

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Wound Healing

Healing process in general involve:

(1) Inflammation

(2) Formation of granulation tissue

(3) ECM deposition and remodeling

The process of wound healing depends on the size of defect i.e. the amount of damaged tissue.

Basically skin wounds are:

- Incised wound (very little tissue loss). These wounds heal by ***first intention*** (primary union)
- Wounds with tissue loss. These wounds heal by ***secondary intention*** (secondary union).

Healing by first intention (primary union):

This type of wound healing occurs when uninfected incision and other clean wounds, (with little damage and without loss of tissue), are closed promptly by surgical suturing.

- **Immediately**, when an incision is made in the skin and the subcutaneous tissue, blood escaping from the cut vessels clots on the wound surface and fills the gap between the wound edges. Then the blood clot will dehydrate and becomes dry forming a protective covering (scab) which effectively seals the wound. Fibrin in the blood clot binds the cut surfaces together.

- Within the **first 2-3 hours** neutrophils start to appear at the margins of the incision moving toward the fibrin clot. The first tissue to bridge the incisional gap is the squamous epithelium of the epidermis. The epidermis at its cut edges thickens as a result of mitotic activity of the epithelial basal cells.

- Within **24 to 48 hours** spurs of epithelial cells from the edges both migrate and grow along the cut margins depositing basement membrane components as they move. They fuse in the mid-line beneath the scab, thus producing continuous but thin epithelial layer. Neutropils present in the area will release lysosomal enzymes that begin digestion of the blood clot.

- Within **2-3 day**s macrophages and lymphocytes have largely replaced the neutrophils. Macrophages will release lysosomal enzymes that begin digestion of the blood clot. The dermis and the subcutaneous tissue are replaced by the formation of granulation tissue, which begins to form in the 3rd day.

- By **day 3** angiogenesis can be observed at the wound margin. At this time fibroblasts begin to proliferate and migrate into the wound. They produce extracellular matrix protein and collagen fibers. Epithelial cell proliferation continues, thickening the epidermal-covering layer.

- By **day 5** the incisional space is filled with granulation tissue. Angiogenssis is maximal. Collagen fibers become more abundant and begin to bridge the incision. The epidermis recovers its normal thickness with surface keratinization.

- During the **second week**, there is continued accumulation of collagen and proliferation of fibroblasts. By about 10 days, the strength of the repair is sufficient to enable removal of sutures. Leukocytic infiltration, edema and increased vascularity have largely disappeared. At this time the process of blanching of healed tissue begins (whitening) due to increased fibrosis with regression of vascular channels.

- By the **third week** the total amount of collagen in the wound has almost reached the maximum. Within this time there will be the replacement of type III by type I collagen.

- By **the end of the first month**, the scar comprises a cellular connective tissue devoid of inflammation, covered by intact epidermis. The dermal appendages destroyed at the line of incision are permanently lost. Tensile strength of the wound increases thereafter, but it may take months for the wounded area to obtain its maximal strength.

- Once the wound has healed the scar is commonly raised above the surface due to the underlying proliferative processes and is red as a result of increased vascularity. The blood vessels gradually decrease in number. Elastic fibers are formed much later than collagen. Sensory nerves may grow into the scar in about three months.

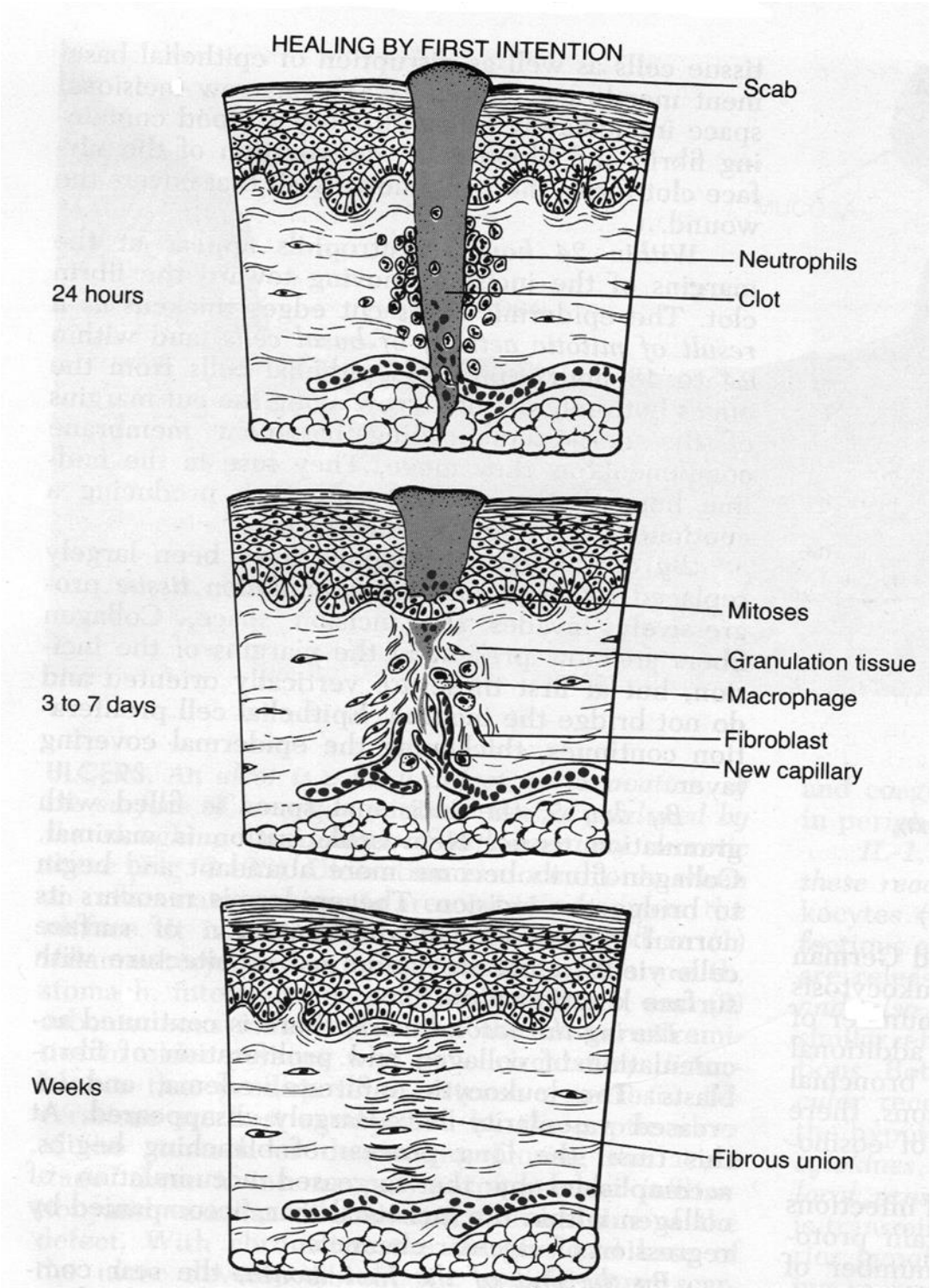


Fig: Shows wound healing by primary intention.

Healing by secondary intention (secondary union):

This type of wound healing occurs in an open wound where there has been loss of tissue (ulceration, necrosis or infection). In this type of healing there is formation of more amounts of granulation tissue, which grow in the base of the wound to fill the defect. It takes longer time than that of primary intention.

- **Immediately,** the defect is filled with blood, blood clots and dries on its surface, forming a scab in some wounds.

- **Soon after,** there is an intense inflammatory reaction in the surrounding tissues with migration of neutropils and subsequently of monocytes (these cells remove the fibrin and other debris on the wound surface.

- **In the first day or two after injury,** epithelial cells at the margins enlarge and begin to proliferate and migrate down the walls of the wound producing a sheet of cells in the form of tongue-like projections. These projections grow beneath the clot or exudate on the wound surface in-between the pre-existing viable connective tissue and the surface clot. Since the denuded area is large, the advancing epithelial sheet does not completely cover the wound until the granulation tissue from the base has started to fill the wound space.

- **Within few days (3-4 days),** the acute inflammation will subside and is replaced by granulation tissue, also the clot in the center of the wound is invaded and replaces by this granulation tissue.

- **In the day 4 after wounding,** granulation tissue starts to form and usually lasts until day 21 depending on the size of the wound.

In the early-formed granulation tissue, the pre-existing vessels in the wound base produce vascular sprouts, which grow upward, adjacent sprouts, connect to form loops near the

wound surface. The connected loops canalize to establish a blood flow. These loops are very fragile and the slightest trauma causes bleeding. At this stage granulation tissue is named as vascular granulation tissue. The process of vascularisation is accompanied by fibroplasia in which there is activation of fibroblasts for production of collagen (type III). The migrating epidermis covers the granulation tissue and in this way a mushroom-shaped scab is formed with a central attachment and finally becomes nipped off.

- **After about two weeks,** the wound surface is covered, the epithelial cell migration ceases and proliferation, stratification and keratinization (i.e. epithelization) are rapidly completed. By time, the regenerated epidermis becomes thicker and sends short process into the underlying tissues, rete ridges and skin appendages are not reformed.

- **After a month,** fibroplasia proceeds and the granulation tissue begins to become mature and there will be more deposition of collagen which is of type I.

At the stage of granulation tissue maturation, there is a process of devascularization, in which some vessels undergo atrophy, some vessels acquire a muscular coat and become arterioles, whilst others enlarge to form thin-walled venules.

Myofibroblasts that are derived from fibroblasts are responsible for wound contraction. They draw the edges of the wound together at a lower level than the surrounding tissue reducing the size of the final scar.

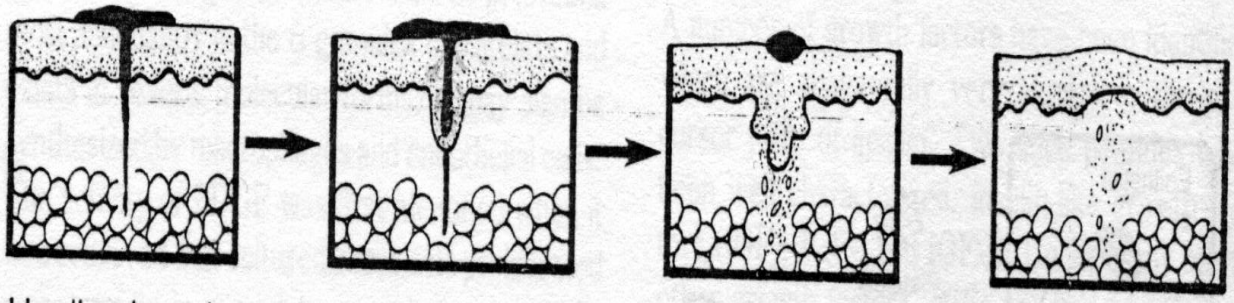
- **Over a period of months** and possibly over a year scar tissue becomes highly collagenized. At this time there will be a remodeling phase involving the collagen and its associated matrix. The proportion of the original fine (type III) collagen is reabsorbed (due to the action of collagenase) and is replaced with type I collagen, which forms broad bands of mature collagen fibers with more cross-links and greater tensile strength.

The secondary intention healing differs from first intention in the following respects:

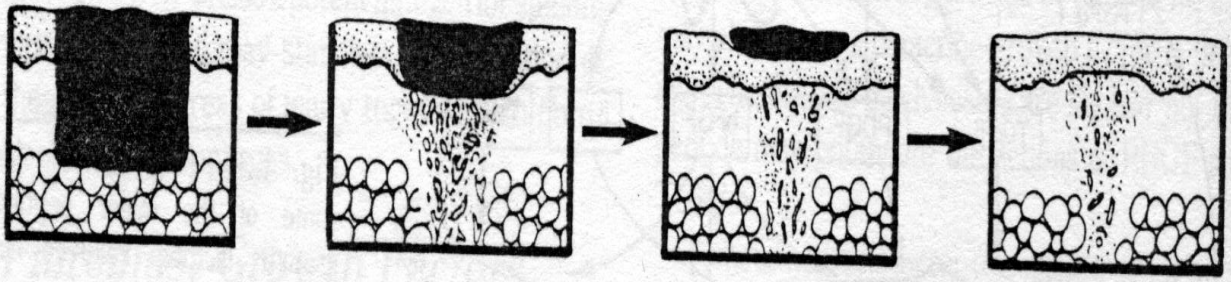
1. Loss of greater amount of tissue.
2. Greater amounts of inflammatory exudate and necrotic debris.
3. Formation of greater amounts of granulation tissue.
4. Wound contraction (contraction of surface wound).
5. Production of larger amount of scar.
6. Loss of skin appendages and rete ridges.

Phase of healing	Days post injury	Cells involved in phase
Bleeding and hemostasis	Immediate	Platelet
Inflammation	Day 1-4	Neutrophils
Proliferation and granulation	Day 4-21	Angiocytes, fibroblast, macrophages, lymphocytes, neurocytes
Contraction	Day 21-	Myofibroblasts, keratinocytes
Remodelling	Day 21-2 yrs	Fibrocytes

Table shows phases of wound healing



Healing by primary intention



Healing by secondary intention

Fig. 4.32 Outline of stages involved in healing of skin wounds. Initially the wound fills with blood clot. This is followed by regeneration of keratinocytes and a connective tissue response (formation of granulation tissue) in the dermis. The basic mechanisms of healing by primary and secondary intention are similar. However, there is a greater connective tissue response in healing by secondary intention and the whole process is much slower.

Factors affecting wound healing

Generally speaking, the types, size, site of the wound are of importance in wound healing, but there are a number of factors that can alter the rate and efficiency of healing. These can be classified into local and systemic factors.

- **Local factors:**
  1. Wound infection.
  2. Poor blood supply.
  3. Excessive movement.
  4. Presence of foreign materials.
  5. Ionized radiation.

- **Systemic factors:**
  1. Nutrition:
     - Protein lack.
     - Vitamin C deficiency.
     - Zinc deficiency.
  2. Chronic debilitating diseases such as Diabetes mellitus, renal failure, malignancies and hematological disorders.
  3. Corticosteroid treatment (hormones).
  4. Systemic infections.

Complications of wound healing

1. Infections.
2. Implantation (epidermoid) cyst.
3. Keloid formation.
4. Wound contraction.
5. Pigmentary changes.
6. Painful scar (traumatic neuroma).
7. Weak scar.

Keloid nodules: Dermal injury is sometimes followed by excessive fibroblasts proliferation and collagen production results in the appearance of raised area of scar tissue called keloid (hypertrophic scar). The cause of this is unknown.