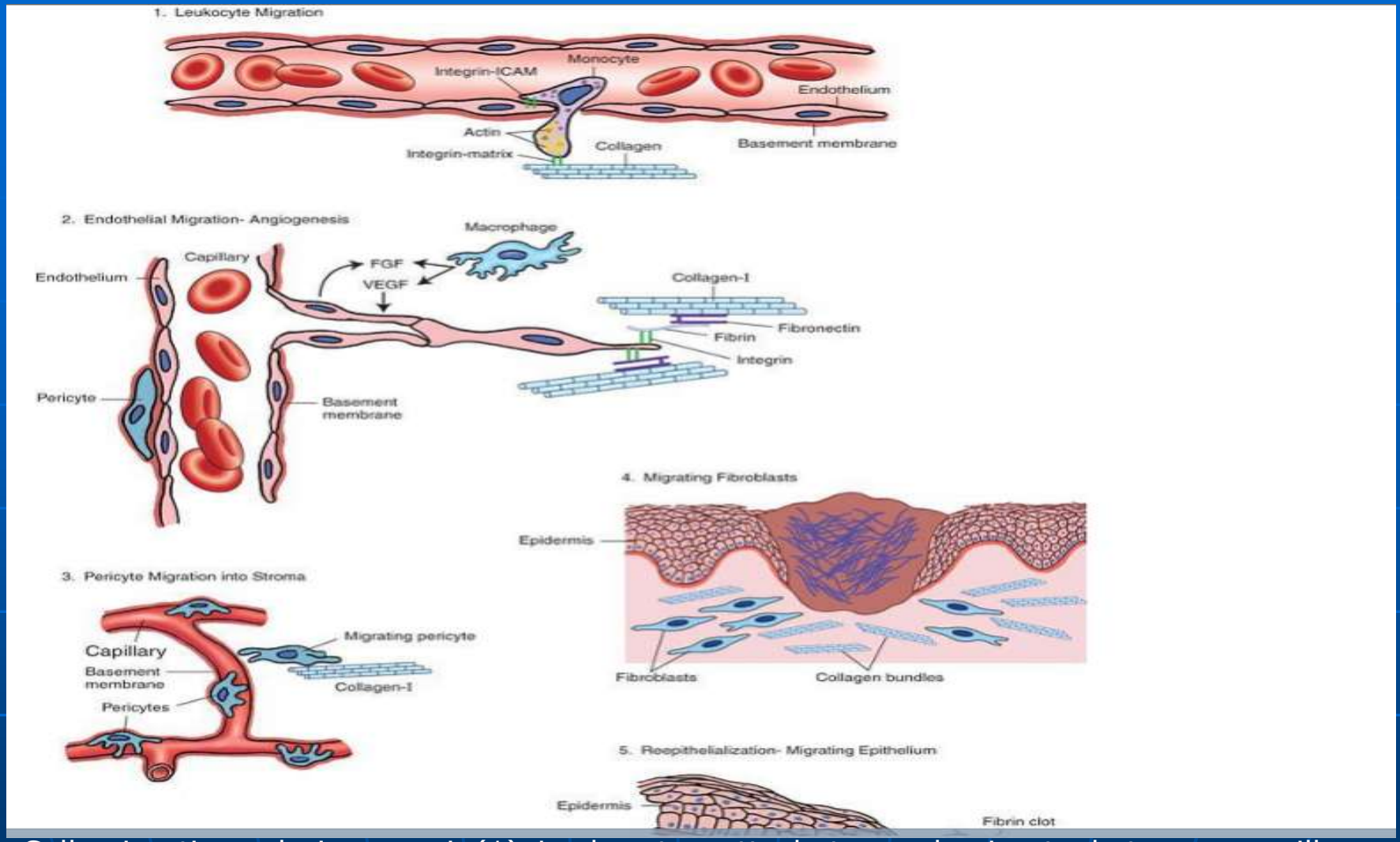
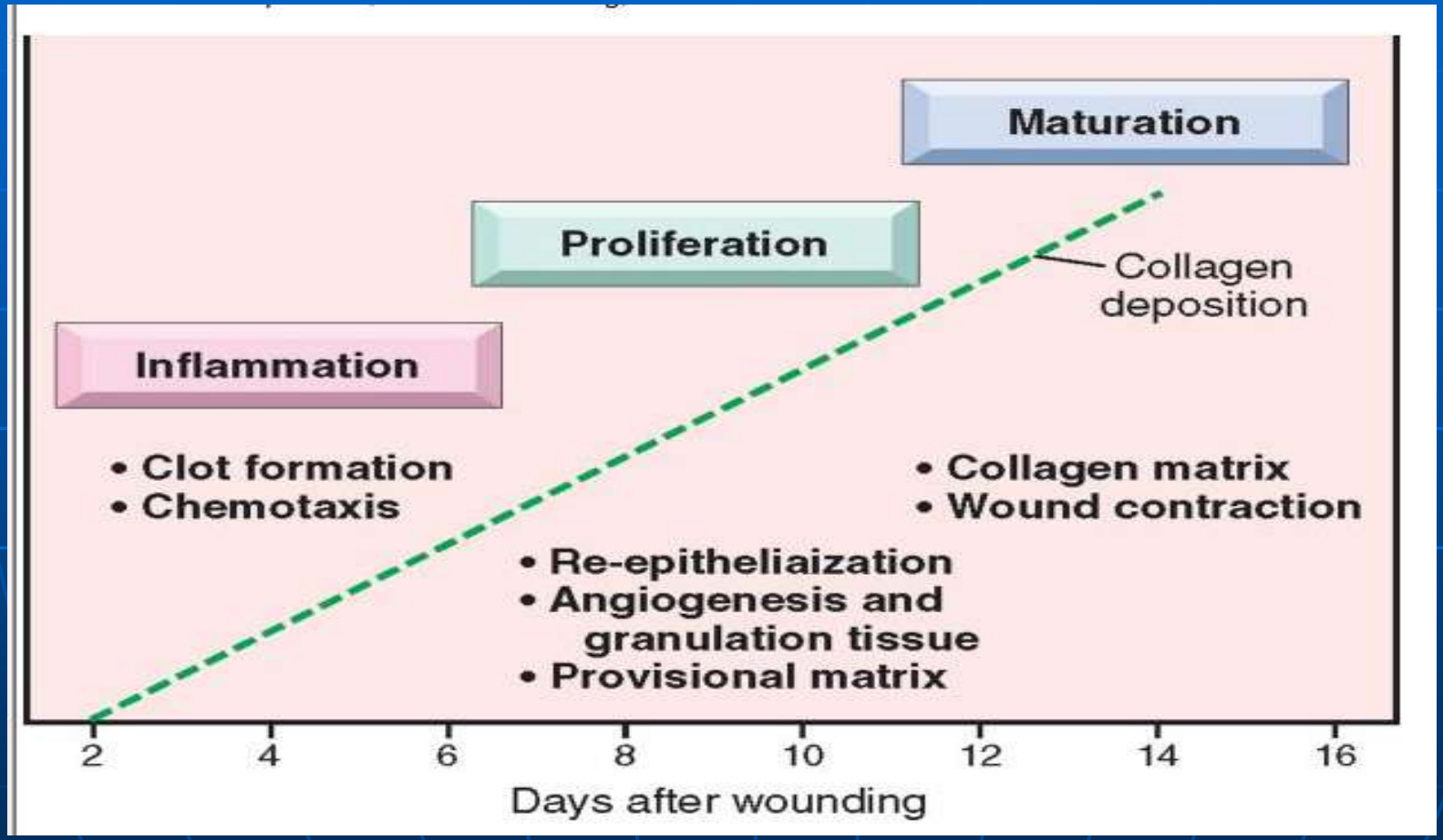
Wound healing



Cell migrations during repair.(1) Leukocytes attach to, and migrate between, capillary endothelial cells, penetrate the basement membrane, and enter the matrix. (2) Capillary endothelial cells, released from the basement membrane, migrate through the matrix to form new capillaries. (3) Pericytes detach from endothelial cells and their basement membranes to migrate into the matrix. (4) Fibroblasts become bipolar and migrate through the matrix to the site of injury. (5) Epithelial keratinocytes detach from neighboring cells and basement membranes and migrate between the scab and the wound along the provisional matrix of the dermis.

Phases of cutaneous wound healing



Clean wound healing

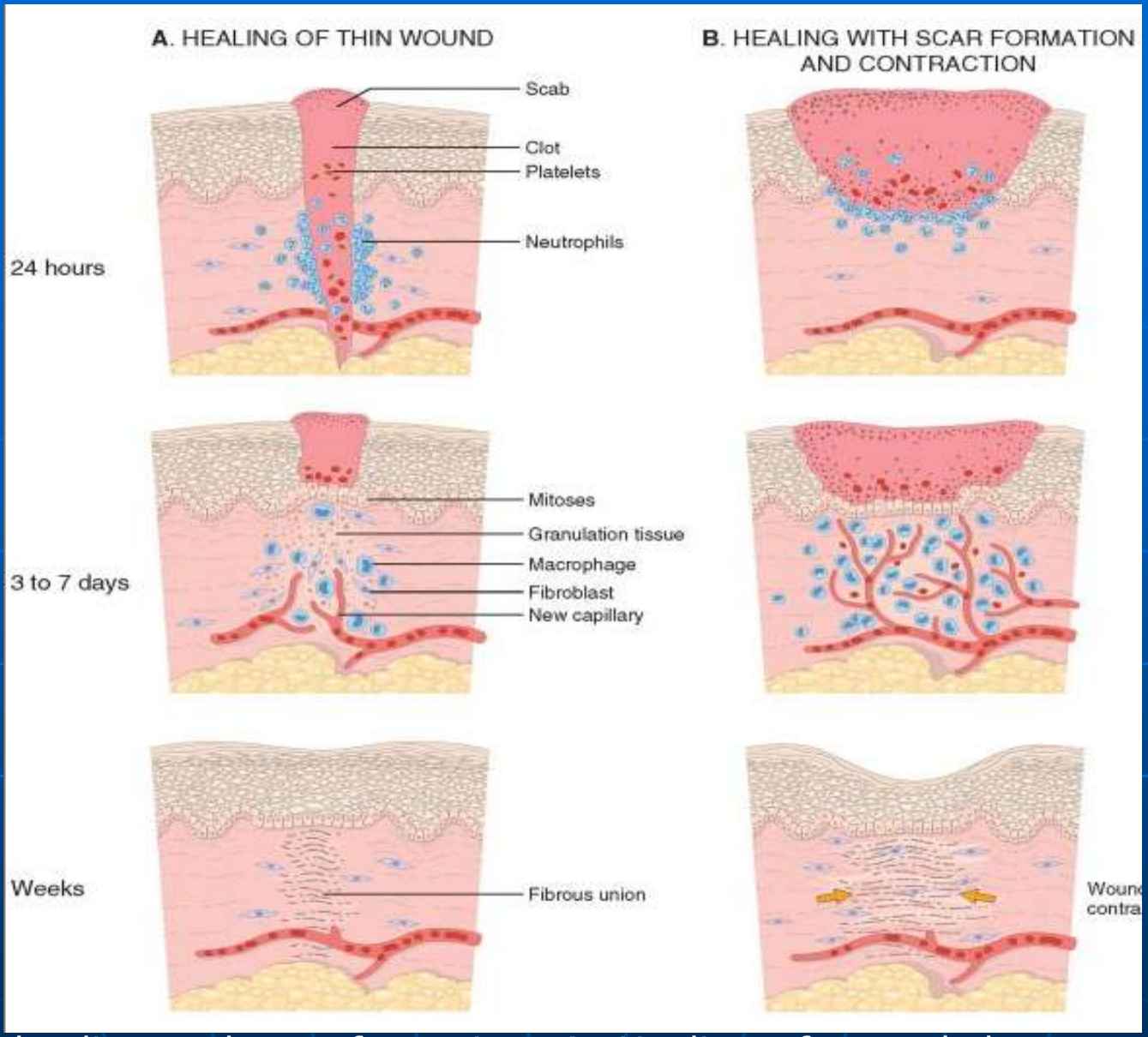
The incision causes death of a limited number of epithelial and connective tissue cells and disruption of epithelial basement membrane continuity.

Re-epithelialization to close the wound occurs with formation of a relatively thin scar.

Healing by secondary union or by second intention

The repair process is more complicated when large defects on the skin surface, causing extensive loss of cells and tissue.

The healing of these wounds involves a more intense inflammatory reaction, the formation of abundant granulation tissue and extensive collagen deposition, leading to the formation of a substantial scar, which generally contracts.



Wound healing and scar formation. A, Healing of wound that caused little loss of tissue: note the small amount of granulation tissue, and formation of a thin scar with minimal contraction. B, Healing of large wound: note large amounts of granulation tissue and scar tissue, and wound contraction.

The sequence of events in wound healing

- Formation of Blood Clot.

- Wounding causes the rapid activation of coagulation pathways, which results in *the formation of a blood clot on the wound surface*.
- In addition to entrapped red cells, the clot contains fibrin, fibronectin, and complement components.
- *The clot serves to stop bleeding and also as a scaffold for migrating cells, which are attracted by growth factors, cytokines and chemokines released into the area*.

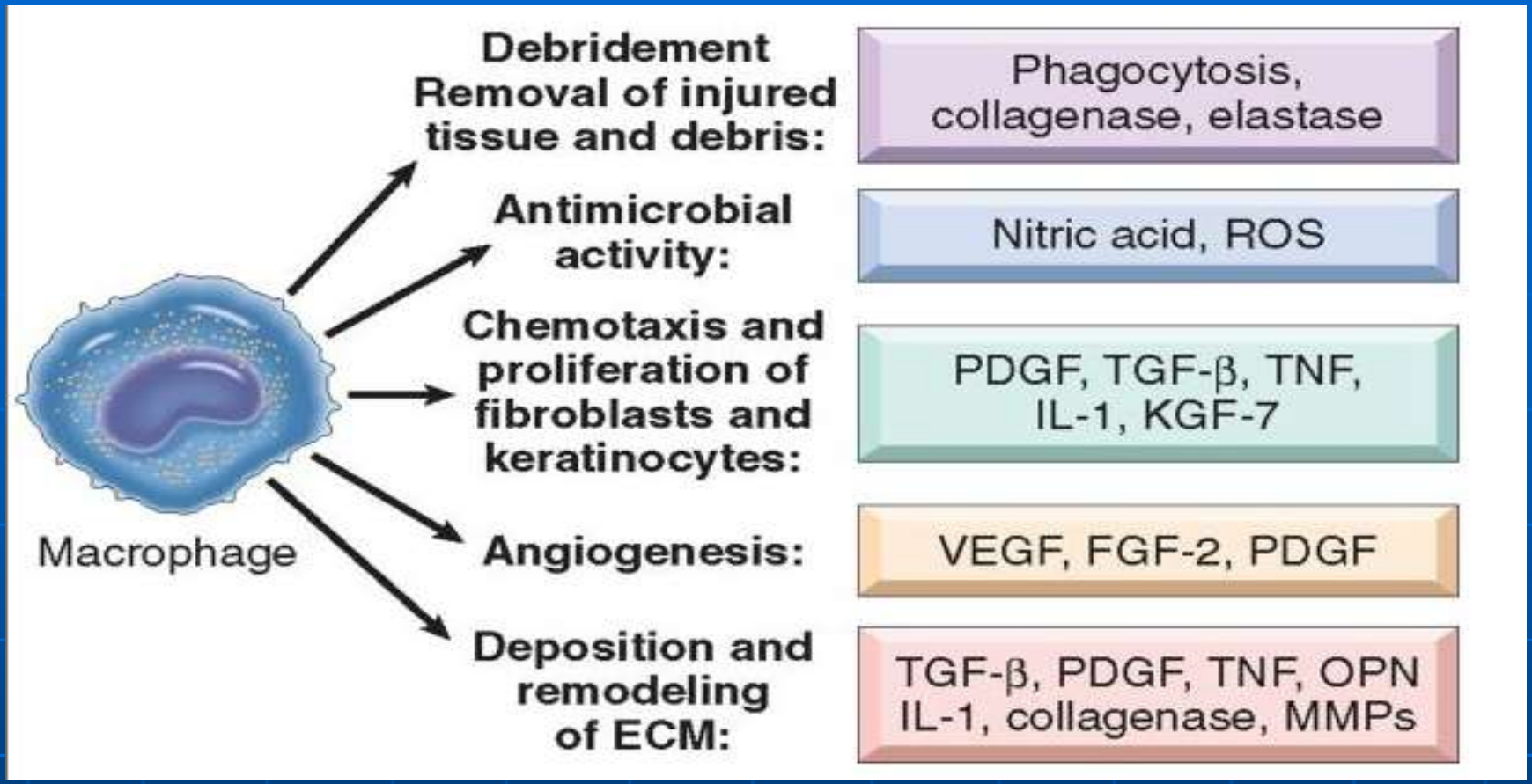
- In wounds causing large tissue deficits, the fibrin clot is larger, and there is more exudate and necrotic debris in the wounded area.

Formation of Granulation Tissue.

- Fibroblasts and vascular endothelial cells proliferate in the first 24 to 72 hours.

- Granulation tissue progressively invades the incision space; the amount of *granulation tissue that is formed depends on the size of the tissue deficit created by the wound and the intensity of inflammation*.

- 5 to 7 days, granulation tissue fills the wound area and neovascularization is maximal.



Multiple roles of macrophages in wound healing. Macrophages participate in wound debridement, have antimicrobial activity, stimulate chemotaxis and the activation of inflammatory cells and fibroblasts, promote angiogenesis, and stimulate matrix remodeling and synthesis.

Scar formation.

The leukocytic infiltrate, edema, and increased vascularity largely disappear during the second week.

Blanching begins, accomplished by the increased accumulation of collagen within the wound area and regression of vascular channels.

The original granulation tissue scaffolding is converted into a pale, avascular scar, composed of spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components.

By the end of the first month, the scar is made up of acellular connective tissue devoid of inflammatory infiltrate, covered by intact epidermis.

Wound Contraction.

Wound contraction generally occurs in large surface wounds. The contraction helps to

- Close the wound by decreasing the gap between dermal edges.
- Reducing the wound surface area.

Myofibroblasts are formed from tissue fibroblasts through the effects of PDGF, TGF-β, and FGF-2 released by macrophages at the wound site, but they can also originate from bone marrow precursors known as fibrocytes, or from epithelial cells, through the process of epithelial-to-mesenchymal transition.

Connective Tissue Remodeling.

The replacement of granulation tissue with a scar involves changes in the composition of the ECM.

The balance between ECM synthesis and degradation results in remodeling of the connective tissue framework – an important feature of tissue repair.

Some of the growth factors that stimulate synthesis of collagen and other connective tissue molecules also modulate the synthesis and activation of metalloproteinases, enzymes that degrade these ECM components.

Recovery of Tensile Strength.

at the end of the first week, wound strength is approximately 10% that of unwounded skin.

Wound strength increases rapidly over the next 4 weeks, slows down at approximately the third month after the original incision, and reaches a plateau at about 70% to 80% of the tensile strength of unwounded skin.

The recovery of tensile strength results from the excess of collagen synthesis over collagen degradation during the first 2 months of healing, and, at later times, from structural modifications of collagen fibers (cross-linking, increased fiber size).

systemic factors that influence wound healing

1. Nutrition: Protein deficiency, for example, and particularly vitamin C deficiency, inhibit collagen synthesis and retard healing.
2. Metabolic status: Diabetes mellitus, is associated with delayed healing, as a consequence of the microangiopathy that is a frequent feature.
3. Circulatory status can modulate wound healing. Inadequate blood supply, usually caused by arteriosclerosis or venous abnormalities (e.g., varicose veins) that retard venous drainage, also impairs healing.
4. Hormones such as glucocorticoids have well-documented anti-inflammatory effects that influence various components of inflammation. These agents also inhibit collagen synthesis.

Local factors that influence healing

1. Infection is the single most important cause of delay in healing, because it results in persistent tissue injury and inflammation.
2. Mechanical factors, such as early motion of wounds, can delay healing, by compressing blood vessels and separating the edges of the wound.
3. Foreign bodies, such as unnecessary sutures or fragments of steel, glass, or even bone, constitute impediments to healing.
4. Size, location, and type of wound.

   Wounds in richly vascularized areas, such as the face, heal faster than those in poorly vascularized ones, such as the foot.

   small incisional injuries heal faster and with less scar formation than large excisional wounds or wounds caused by blunt trauma.

Complications in wound healing

(1) Deficient scar formation.
(2) Excessive formation of the repair component.
(3) Formation of contractures.