WOUND HEALING

Healing of skin wounds provides a classical example of combination of regeneration and repair described above. This can be accomplished in one of the following two ways:

- Healing by first intention (primary union): and
- Healing by second intention (Secondary union)

Healing by First Intention (Primary Union)

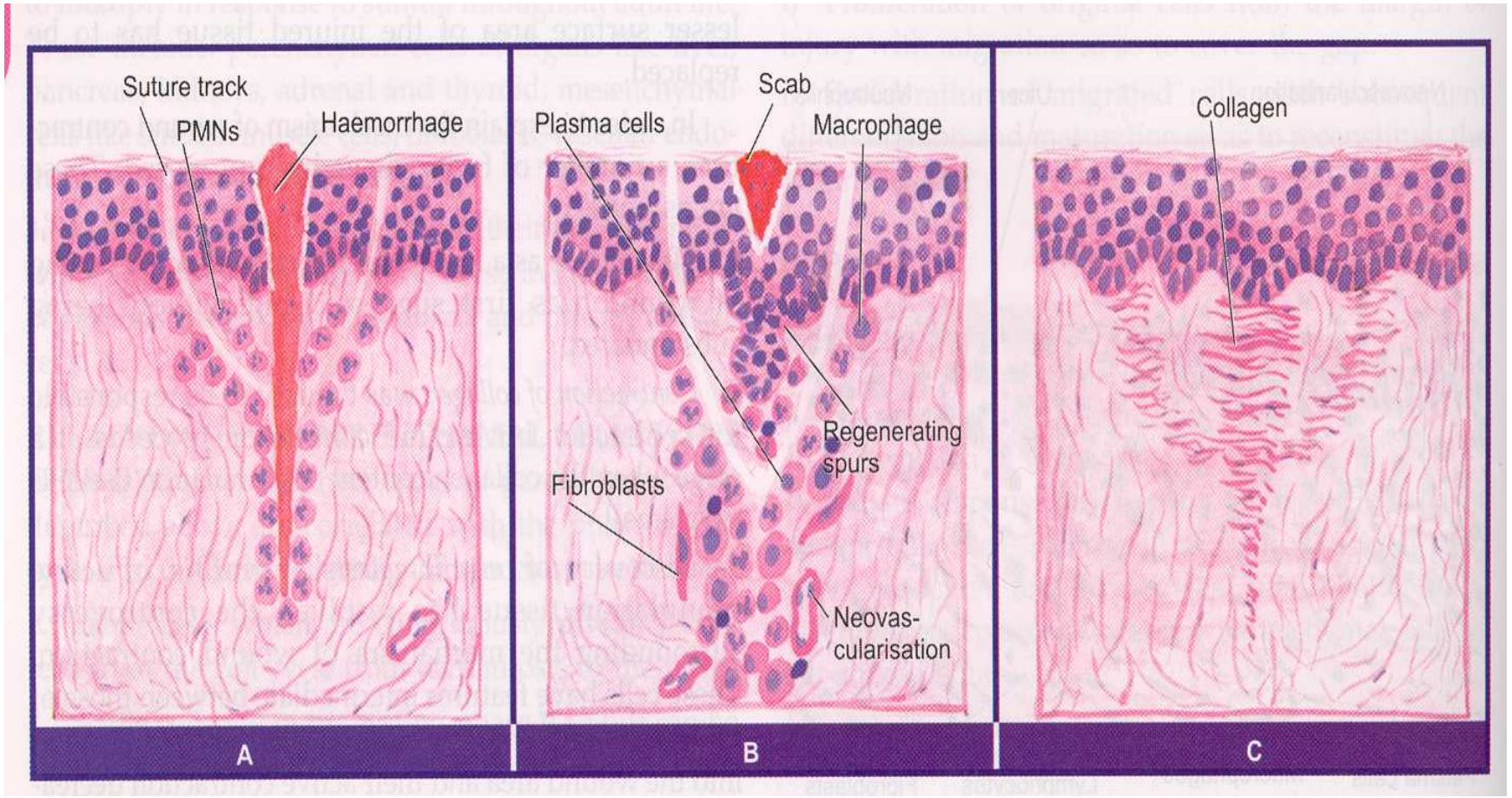
This is defined as healing of a wound which has the following characteristics:

i) Clean and uninfected;

ii) Surgically incised;

iii) Without much loss of cells and tissue; and

iv) Edges of wound are approximated by surgical sutures


Suture track
PMNs
Haemorrhage
A
Scab
Plasma cells
Macrophage
Regenerating spurs
Fibroblasts
Neovas-cularisation
B
Collagen
C

WOUND HEALING

The sequence of events in primary union are described below:

1. **Initial haemorrhage:** Immediately after injury, the space between the approximated surfaces of incised wound is filled with blood which then clots and seals the wound against dehydration and infection.
2. **Acute inflammatory response:** This occurs within 24 hours with appearance of polymorphs from the margins of incision. By 3rd day, polymorphs are replaced by macrophages
3. **Epithelial changes:** The basal cells of epidermis from both the cut margins start proliferating and migrating towards incisional space in the form of epithelial spurs. A well-approximated wound is covered by a layer of epithelium in 48 hours. The migrated epidermal cells separate the underlying viable dermis from the overlying necrotic material and clot, forming scab which is cast off. The basal cells from the margins continue to divide. By 5th day, a multilayered new epidermis is formed which is differentiated into superficial and deeper layers.

WOUND HEALING

4. **Organization:** By 3rd day, fibroblasts also invade the wound area. By 5th day, new collagen fibrils start forming which dominate till healing is completed. In 4 weeks, the scar tissue with scanty cellular and vascular elements, a few inflammatory cells and epithelialised surface is formed.
5. **Suture tracks:** Each suture track is a separate wound and incites the same phenomena as in healing of the primary wound i.e. filling the space with haemorrhage, some inflammatory cell reaction, epithelial cell proliferation along the suture track from both margins, fibroblastic proliferation and formation of young collagen. When sutures are removed around 7th day, much of epithelialised suture track is avulsed and the remaining epithelial tissue in the track is absorbed. However, sometimes the suture track gets infected (stitch abscess) or the epithelial cells may persist in the track (implantation or epidermal cysts).

Thus, the scar formed in a sutured wound is neat due to close apposition of the margins of wound; the use of adhesive tapes avoids removal of stitches and its complications.

Healing by Second Intention (Secondary Union)

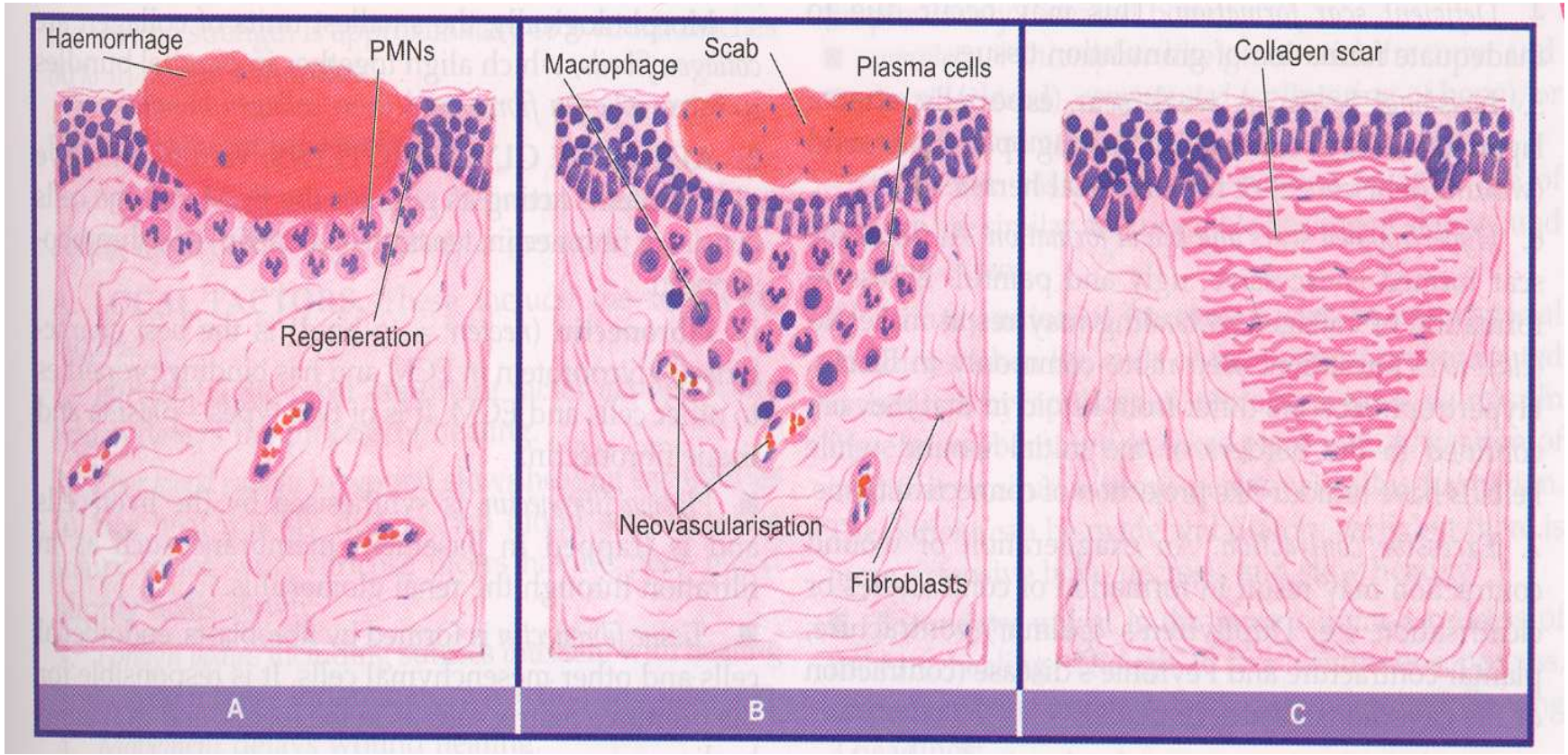
This is defined as healing of a wound having the following characteristics:

i. Open with a large tissue defect, at times infected;

ii. Having extensive loss of cells and tissues, and

iii. The wound is not approximated by surgical sutures but is left open.

The basic events in secondary union are similar to primary union but differ having a larger tissue defect which has to be bridged. Hence healing takes place from the base upwards as well as from the margins inwards. The healing by second intention is slow and results in a large, at times ugly, scar as compared to rapid healing and neat scar of primary union.


Haemorrhage
PMNs
Regeneration
A
Macrophage
Scab
Plasma cells
Neovascularisation
Fibroblasts
B
Collagen scar
C

Healing by Second Intention (Secondary Union)

The sequence of events in secondary union are described below:

1. **Initial haemorrhage:** As a result of injury, the wound space is filled with blood and fibrin clot which dries.
2. **Inflammatory phase:** There is an initial acute inflammatory response followed by appearance of macrophages which clear off the debris as in primary union.
3. **Epithelial changes:** As in primary healing, the epidermal cells from both the margins of wound proliferate and migrate into the wound in the form of epithelial spurs till they meet in the middle and re-epithelialise the gap completely. However, the proliferating epithelial cells do not cover the surface fully until granulation tissue from base has started filling the wound space. In this way, pre-existing viable connective tissue is separated from necrotic material and clot of the surface, forming scab which is cast off. In time, the regenerated epidermis becomes stratified and keratinized.

Healing by Second Intention (Secondary Union)

4. **Granulation tissue:** The main bulk of secondary healing is by granulations. Granulation tissue is formed by proliferation of fibroblasts and neovascularisation from the adjoining viable elements. The newly-formed granulation tissue is deep red, granular and very fragile. With time, the scar on maturation becomes pale and white due to increase in collagen and decrease in vascularity. The specialized structures of skin like hair follicles and sweat glands are not replaced unless their viable residues remain which may regenerate.
5. **Wound contraction:** Contraction of wound is an important feature of secondary healing, not seen in primary healing. Due to the action of myofibroblasts present in granulation tissue, the wound contracts to one-third to one-fourth of its original size. Wound contraction occurs at a time when active granulation tissue is being formed.

Healing by Second Intention (Secondary Union)

6. **Presence of infection:** Bacterial contamination of an open wound delays the process of healing due to release of bacterial toxins that provoke necrosis, suppuration and thrombosis. Surgical removal of dead and necrosed tissue, debridement, helps in preventing the bacterial infection of open wounds.

Complication of Wound Healing

During the course of healing, following complications may occur:

1. **Infection** of wound due to entry of bacteria delays the healing.
2. **Implantation** (epidermal) cyst formation may occur due to persistence of epithelial cells in the wound after healing.
3. **Pigmentation:** Healed wounds may at times have rust-like colour due to staining with haemosiderin. Some coloured particulate material left in the wound may persist and impart colour to the healed wound.
4. **Deficient scar formation.** This may occur due to inadequate formation of granulation tissue.
5. **Incisional hernia.** A weak scar, especially after a laparotomy, may be the site of bursting open of a wound (wound dehiscence) or an incisional hernia.

Complication of Wound Healing

6. **Hypertrophied scars** and keloid formation. At times the scar formed is excessive, ugly and painful. Excessive formation of collagen in healing may result in keloid (claw-like) formation, seen more commonly in blacks. Hypertrophied scars differ from keloid in that they are confined to the borders of the initial wound while keloids have tumour-like projection of connective tissue.
7. **Excessive contraction.** An exaggeration of wound contraction may result in formation of contractures or cicatrisation e.g. Dupuytren's (palmar) contracture, plantar contracture and Peyronie's disease (contraction of the cavernous tissue of penis).
8. **Neoplasia.** Rarely, scar may be the site for development of carcinoma later e.g. squamous cell carcinoma in marjolin's ulcer i.e. a scar following burns on the skin.

Extracellular Matrix – Wound Strength

The wound is strengthened by proliferation of fibroblasts and myofibroblasts which get structural support from the extracellular matrix (ECM). In addition to providing structural support, ECM can direct cell migration, attachment, differentiation and organisation.

ECM has five main components: collagen, adhesive glycoproteins, basement membrane, elastic fibers, and proteoglycans.

Extracellular Matrix – Wound Strength

1. **COLLAGEN.** The collagens are a family of proteins which provide structural support to be multicellular organism. It is the main component of tissues such as fibrous tissue, bone, cartilage, valves of heart, cornea, basement membrane etc.

Collagen is synthesized and secreted by a complex biochemical mechanism on ribosomes. The collagen synthesis is stimulated by various growth factors and is degraded by collagenase. Regulation of collagen synthesis and degradation take place by various local and systemic factors so that the collagen content of normal organs remains constant. On the other hand, defective regulation of collagen synthesis leads to hypertrophied scar, fibrosis, and organ dysfunction.

Extracellular Matrix – Wound Strength

Depending upon the biochemical composition, 18 types of collagen have been identified called collagen type I to XVIII, many of which are unique for specific tissues. Type I, III and V are true fibrillar collagen which form the main portion of the connective tissue during healing of wounds in scars. Other types of collagen are non-fibrillar and amorphous material seen as component of the basement membranes.

Morphologically, the smallest units of collagen are collagen fibrils, which align together in parallel bundles to form collagen fibers, and then collagen bundles.

Extracellular Matrix – Wound Strength

2. **ADHESIVE GLYCOPROTEINS.** Various adhesive glycoproteins acting as glue for the ECM and the cells consist of fibronectin, tenascin (cytotactin) and thrombospondin.

i. **Fibronectin** (nectere = to bind) is the best characterized glycoprotein in ECM and has binding properties to other cells and ECM. It is of two types – plasma and tissue fibronectin.

Plasma fibronectin is synthesized by t he liver cells and is trapped in basement membrane such as infiltration through the renal glomerulus.

Tissue fibronectin is formed by fibroblasts, endothelial cells and other mesenchymal cells. It is responsible for the rpimitive matrix such as in the foetus, and in wound healing.

Extracellular Matrix – Wound Strength

ii. **Tenascin or cytotactin** is the glycoprotein associated with fibroblasts and appears in wound about 48 hours after injury. It disappears from mature scar tissue.

iii. **Thrombospondin** is mainly synthesised by granules of platelets. It functions as adhesive protein for keratinocytes and platelets but is inhibitory to attachment of fibroblasts and endothelial cells.

3. **BASEMENT MEMBRANE.** Basement membranes are periodic acid-Schiff (PAS)-positive amorphous structures that lie underneath epithelia of different organs and endothelial cells. They consist of collagen type IV and laminin.

4. **ELASTIC FIBRES.** While the tensile strength in tissue comes from collagen, the ability to recoil is provided by elastic fibers. Elastic fibers consist of 2 components – elastin glycoprotein and elastic microfibril. Elastases degrade the elastic tissue e.g. in inflammation, emphysema etc.

Extracellular Matrix – Wound Strength

5. **PROTEOGLYCANS.** These are a group of molecules having 2 components – and essential carbohydrate polymer (called polysaccharide or glycosaminoglycan), and a protein bound to it, and hence the name proteoglycan. Various proteoglycans are distributed in different tissues as under:

i) **Chondroitin sulphate** – abundant in cartilage, dermis.

ii) **Heparan sulphate** – in basement membranes

iii) **Dermatan sulphate** – in dermis

iv) **Keratan sulphate** – in cartilage.

v) **Hyaluronic acid** – in cartilage, dermis

In would healing, the deposition of proteoglycans precedes collagen laying.

The strength of wound also depends upon factors like the site of injury, depth of incision and area of wound. After removal of stitches on around 7^{th} day, the wound strength is approximately 10% which reaches 80% in about 3 months.

Factoring influencing healing

Two types of factors influence the wound healing: those acting locally, and those acting in general.

A. LOCAL FACTORS. These include the following factors:

1. Infection is the most important factor acting locally which delays the process of healing.
2. Poor blood supply to wound slows healing e.g. injuries to face heal quickly due to rich blood supply while injury to leg with varicose ulcers having poor blood supply heals slowly.
3. Foreign bodies including sutures interfere with healing and cause intense inflammatory reaction and infection.
4. Movement delays wound healing.
5. Exposure to ionising radiation delays granulation tissue formation.
6. Exposure to ultraviolet light facilitates healing.
7. Type, size and location of injury determines whether healing takes place by resolution or organisation.

Factoring influencing healing

B. SYSTEMIC FACTORS. These are as under:

1. **Age.** Wound healing is rapid in young and somewhat slow in aged and debilitated people due to poor blood supply to the injured area in the latter.
2. **Nutrition.** Deficiency of constituents like proteins, vitamin C (scurvy) and zinc delays the wound healing.
3. **Systemic infection** delays wound healing.
4. **Administration of glucocorticoids** has anti-inflammatory effect.
5. **Uncontrolled diabetics** are more prone to develop infections and hence delay in healing.
6. **Haematologic abnormalities** like defect of neutrophil functions (chemotaxis and phagocytosis), and neutropenia and bleeding disorders slow the process of wound healing.

BONE HEALING

A fracture is usually accompanied by damage to or haemorrhage into adjacent soft tissues which are repaired by the process of organization, while the bone is repaired by regeneration.

EVENTS FOLLOWING A FRACTURE

1] Immediate effects

* Necrosis of ends of bone.
* Damage to soft tissues with hemorrhage (hematoma) and fibrin deposition.

2] Early reaction-inflammatory

* First 4-5 days.
* Phagocytosis of debris and necrotic tissues.
* Early organization: capillaries and fibroblasts.

3] Formation of callus (early bone regeneration)

* After 1 week.
* Resorption in healthy bone.
* Provisional callus bridges the gap – first, osteoid tissue (may include cartilage) then woven bone.

4] Mature callus

* From 3 weeks onwards.
* Cortical gap healed by ossification.
* Osteoblastic and osteoclastic activity proceeding.

5] Remodelling of callus

* Definitive – weeks into months.
* Osteoblasts and osteoclasts active.

6] Final reconstruction

* Months later.
* Fracture site may be almost invisible.

COMPLICATIONS

1] Fat embolism may occur in fracture of long bones due to entry of fat from the marrow cavity into the torn ends of veins.

2] Infection – if the overlying skin is breached.

PATHOLOGICAL FRACTURE

- When the break occurs at the site of pre-existing disease of the bone.
- A common condition is a secondary tumor growing in and destroying the bone.
- Mixture of tumor and hematoma – healing inhibited.

FACTORS INFLUENCING HEALING OF FRACTURES

1. Local factors
   a. Infection
   b. Pathological fracture
   c. Poor apposition and alignment
   d. Continuing movement of bone ends
   e. Poor blood supply

Poor blood supply (contd)

This is largely influenced by the anatomical site of the fracture, for example:

a. Nutrient artery damaged by fracture.
b. Fracture through area devoid of periosteum (e.g. neck of femur).
c. Minimal adjacent soft tissue (e.g.tibia).

2. General factors

a. Old age
b. Poor nutrition