Healing

Healing is the body response to injury in an attempt to restore the normal structure and function. Healing involves 2 distinct processes:

1) *Regeneration* when healing takes place by proliferation of parenchymal cells and usually results in complete restoration

of the original tissues.

2) *Repair* when healing takes place by proliferation of connective tissue elements resulting in fibrosis and scarring.

At times, both the processes take place simultaneously.

REGENERATION:

Some parenchymal cells are short-lived while others have alonger lifespan. In order to maintain proper structure of tissues, these cells are under the constant regulatory control of their cell cycle. These include growth factors such as:
epidermal growth factor, fibroblast growth factor, platelet derived growth factor, endothelial growth factor,
transforming growth factor-
Regeneration of any type of parenchymal cells involves the following 2 processes:

i) Proliferation of original cells from the margin of injury with migration so as to cover the gap.
ii) Proliferation of migrated cells with subsequent differentiation and maturation so as to reconstitute the original tissue.

REPAIR

Repair is the replacement of injured tissue by fibrous tissue.Two processes are involved in repair:
1. Granulation tissue formation; and 2. Contraction of wounds.
Repair response takes place by participation of mesenchymal cells (consisting of connective tissue stem cells,fibrocytes and histiocytes), endothelial cells, macrophages,platelets, and the parenchymal cells of the injured organ.

Granulation Tissue Formation

The term granulation tissue derives its name from slightly granular and pink appearance of the tissue. Each granule corresponds histologically to proliferation of new small blood vessels which are slightly lifted on the surface by thin covering of fibroblasts and young collagen. The following 3 phases are observed in the formation of granulation tissue

1. Phase Of Inflammation. Following trauma, blood clots at the site of injury. There is acute inflammatory response with exudation of plasma, neutrophils and some monocytes within 24 hours.

2.Phase Of Clearance. Combination of proteolytic enzymes liberated from neutrophils, autolytic enzymes from dead tissues cells, and phagocytic activity of macrophages clear off the necrotic tissue, debris and red blood cells.

3. Phase Of Ingrowth Of Granulation Tissue. This phase consists of 2 main processes: angiogenesis or neovascularisation, and fibrogenesis.

i) Angiogenesis (neovascularisation). Formation of new blood vessels at the site of injury takes place by proliferation of endothelial cells from the margins of severed blood vessels .Initially, the proliferated endothelial cells are solid buds but within a few hours develop a lumen and start carrying blood. The newly formed blood vessels are more leaky, accounting for the oedematous appearance of new granulation tissue .Soon, these blood vessels differentiate into muscular arterioles, thin-walled venules and true capillaries.The process of angiogenesis is stimulated with proteolytic destruction of

basement membrane. Angiogenesis takes place under the influence of following factors:

a) Vascular endothelial growth factor (VEGF) elaborated by mesenchymal cells while its receptors are present in endothelial cells only.

b)Platelet-derived growth factor (PDGF), transforming growth factor- (TGF-), basic fibroblast growth factor

all associated with cellular proliferation.

ii) Fibrogenesis. The newly formed blood vessels are present in an amorphous ground substance or matrix.The new fibroblasts originate from fibrocytes as well as by mitotic division of fibroblasts. Some of these fibroblasts have combination of morphologic and functional characteristics of smooth muscle cells (*myofibroblasts*). Collagen fibrils begin to appear by about 6th day. As maturation proceeds, more and more of collagen is formed while the number of active fibroblasts and new blood vessels decreases. .

Contraction of Wounds

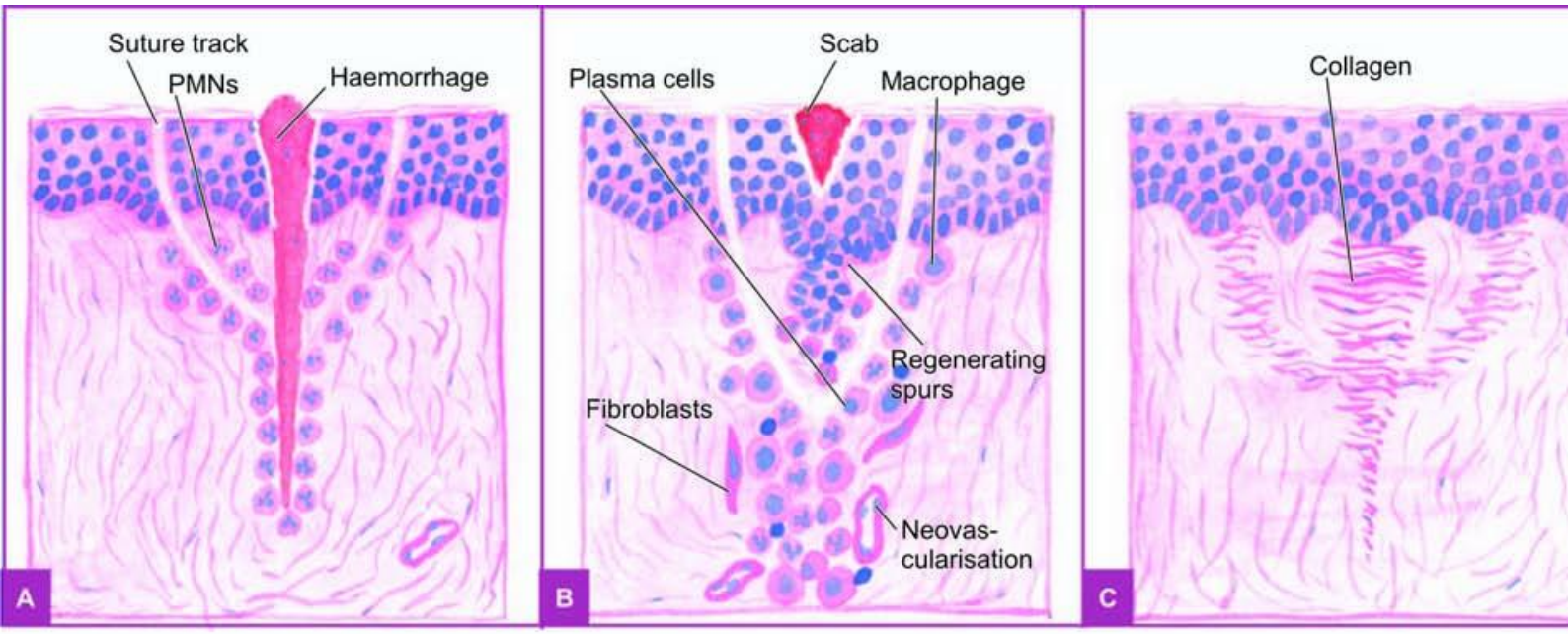
The wound starts contracting after 2-3 days and the process is completed by the 14th day. During this period, the wound is reduced by approximately 80% of its

original size.Contracted wound results in rapid healing since lesser surface area of the injured tissue has to be replaced.

WOUND HEALING

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

Healing by first intention *(primary union)*
Healing by second intention *(secondary union)*.



Primary union of skin wounds:
A, The incised wound as well as suture track on either side are filled with blood clot and there is inflammatory response from the margins.
B, Spurs of epidermal cells migrate along the incised margin on either side as well as around the suture track. Formation of granulation tissue also begins from below.
C, Removal of suture at around 7th day results in scar tissue at the sites of incision and suture track.

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.
The sequence of events in primary union is illustrated in

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 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.

4. Organisation. 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. 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 in 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. The sequence of events in secondary union is illustrated
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 inflam-matory 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

4. Granulation tissue. 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. Specialised structures of the 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.

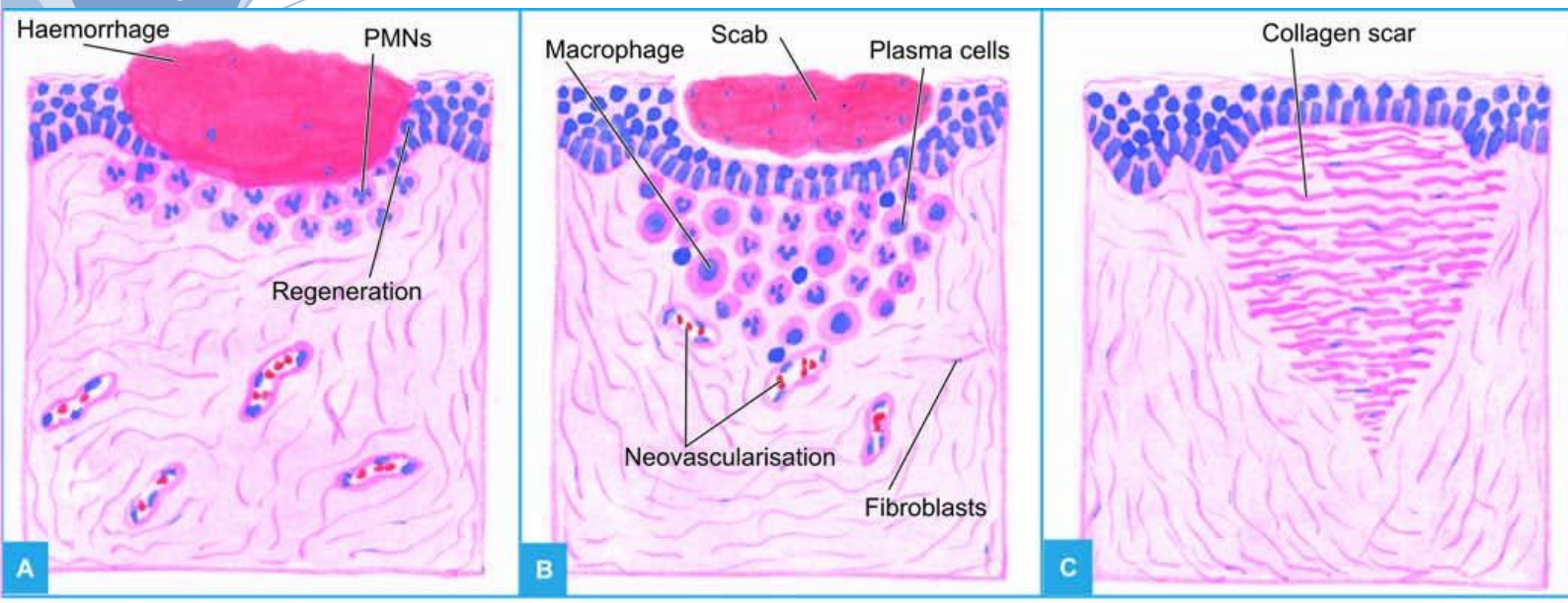
6. Presence of infection. Bacterial contamination of an open wound delays

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

Complications 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.



Secondary union of skin wounds.

A, The open wound is filled with blood clot and there is inflammatory response at the junction of viable tissue.

B, Epithelial spurs from the margins of wound meet in the middle to cover the gap and separate the underlying viable tissue from necrotic tissue at the surface forming scab.

C, After contraction of the wound, a scar smaller than the original wound is left.

Differences between primary and secondary union of wounds are given in Flowing Table

1. Cleanliness of wound	Clean
2. Infection Generally	uninfected
3. Margins	Surgical clean
4. Sutures	Used
5. Healing	Scanty granulation tissue at the incised
6. Outcome	Neat linear scar
7. Complications	Infrequent, epidermal inclusion cyst formation