HEALING

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

Regeneration when healing takes place by proliferation of parenchymal cells and usually results in complete restoration of the original tissues.

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 a longer 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, plateletderived growth factor, endothelial growth factor, transforming growth factor-β. Not all cells of the body divide at the same pace. Some mature cells do not divide at all while others complete a cell cycle every 16-24 hours.

Depending upon their capacity to divide, the cells of the body can be divided into 3 groups: labile cells, stable cells, and permanent cells.

1. Labile cells. These cells continue to multiply throughout life under normal physiologic conditions. These include: surface epithelial cells of the epidermis, alimentary tract, respiratory tract, urinary tract, vagina, cervix, uterine endometrium, haematopoietic cells of bone marrow and cells of lymph nodes and spleen.

2. Stable cells. the capacity to multiply in response to stimuli throughout adult life. These include: parenchymal cells of organs like liver, pancreas, kidneys, adrenal and thyroid; mesenchymal cells like smooth muscle cells, fibroblasts, vascular endothelium, bone and cartilage cells.

3. Permanent cells. These cells lose their ability to proliferate around the time of birth. These include: neurons of nervous system, skeletal muscle and cardiac muscle cells.

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

b) Platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF) and surface integrins are all associated with cellular proliferation.

ii) Fibrogenesis. 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. This results in formation of inactive looking scar known as cicatrisation.

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).

Healing by First Intention (Primary Union) This is defined as healing of a wound which has the following characteristics:

1. clean and uninfected;
2. ii) surgically incised;
3. iii) without much loss of cells and tissue; and
4. iv) edges of wound are approximated by surgical sutures.

The sequence of events in secondary union is illustrated

1. Initial haemorrhage. Immediately after injury, the space between the approximated surfaces of incised wound is filled with blood which then clots and the wound against dehydration and infection.
2. 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 wellapproximated 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.

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.

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Healing by Second Intention (Secondary Union) This is defined as healing of a wound having the following characteristics:

1. open with a large tissue defect, at times infected;
2. ii) having extensive loss of cells and tissues; and
3. 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. 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.
4. Initial haemorrhage. As a result of injury, the wound space is filled with blood and fibrin clot which dries.
5. 2. Inflammatory phase. There is an initial acute inflammatory response followed by appearance of macrophages which clear off the debris as in primary union.
6. 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 forming scab which is cast off. In time, the regenerated epidermis becomes stratified and keratinised.

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 onefourth of its original size.

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.

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.

7. Excessive contraction

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.

Factors Influencing Healing

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

A. LOCAL 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.

B. SYSTEMIC FACTORS:

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 protein, 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.