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اسم المحاضرة الأولى باللغة الإنكليزية : **HEALING**

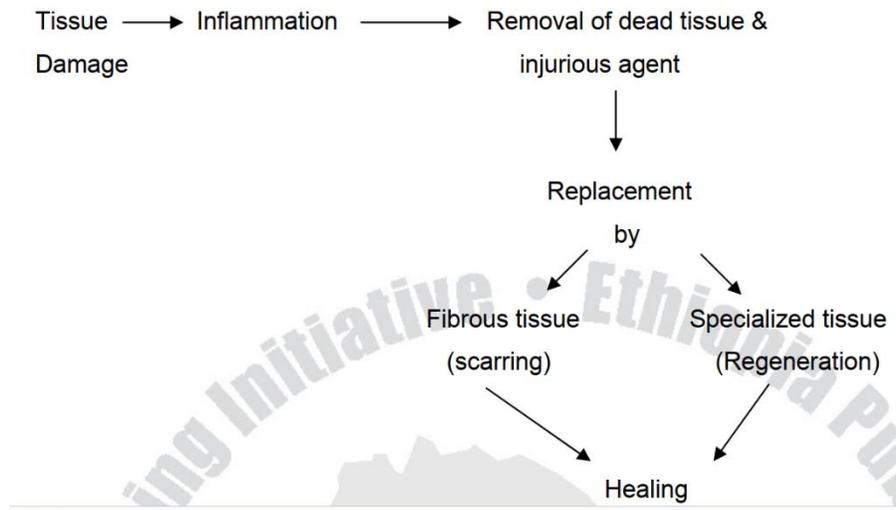
### Definition of healing

The word healing, used in a pathological context, refers to the body's replacement of destroyed tissue by living tissue

### Processes of healing:

**The healing process involves two distinct processes:**

- Regeneration, the replacement of lost tissue by tissues similar in type and
- Repair (healing by scarring), the replacement of lost tissue by granulation tissue which matures to form scar tissue. Healing by fibrosis is inevitable when the surrounding specialized cells do not possess the capacity to proliferate.



Whether healing takes place by regeneration or by repair (scarring) is determined partly by the type of cells in the damaged organ & partly by the destruction or the intactness of the stromal frame work of the organ. Hence, it is important to know the types of cells in the body.

**types of cells Based on their proliferative capacity there are three types of cells.**

### **1. Labile cells**

These are cells which have a continuous turn over by programmed division of stem cells. They are found in the surface epithelium of the gastrointestinal tract, urinary tract or the skin. The cells of lymphoid and haemopoietic systems are further examples of labile cells. The chances of regeneration are excellent.

### **2. Stable cells**

Tissues which have such type of cells have normally a much lower level of replication and there are few stem cells. However, the cells of such tissues can undergo rapid division in response to injury. For example, mesenchymal cells such as smooth muscle cells, fibroblasts, osteoblasts and endothelial cells are stable cells which can proliferate. Liver, endocrine glands and renal tubular epithelium has also such type of cells which can regenerate. Their chances of regeneration are good.

### **3. Permanent cells**

These are non-dividing cells. If lost, permanent cells cannot be replaced, because they do not have the capacity to proliferate. For example: adult neurons, striated muscle cells, and cells of the lens.

**Having been introduced to the types of cells, we can go back to the two types of healing processes & elaborate them.**

#### **a. Healing by regeneration**

Definition: Regeneration (generate=bring to life) is the renewal of a lost tissue in which the lost cells are replaced by identical ones.

#### **Regeneration involves two processes**

1. Proliferation of surviving cells to replace lost tissue
2. Migration of surviving cells into the vacant space.

**The capacity of a tissue for regeneration depends on its**

- 1) proliferative ability,

- 2) degree of damage to stromal framework and
- 3) on the type and severity of the damage.

Tissues formed of labile and stable cells can regenerate provided that stromal framework are intact.

**b. Repair (Healing by connective tissue)**

Definition: - Repair is the orderly process by which lost tissue is eventually replaced by a scar.

A wound in which only the lining epithelium is affected heals exclusively by regeneration. In contrast, wounds that extend through the basement membrane to the connective tissue, for example, the dermis in the skin or the sub-mucosa in the gastrointestinal tract, lead to the formation of granulation tissue and eventual scarring. Tissues containing terminally differentiated (permanent) cells such as neurons and skeletal muscle cells can not heal by regeneration. Rather the lost permanent cells are replaced by formation of granulation tissue.

**In granulation-tissue formation, three phases may be observed.**

**1. Phase of inflammation**

At this phase, inflammatory exudate containing polymorphs is seen in the area of tissue injury. In addition, there is platelet aggregation and fibrin deposition.

**2. Phase of demolition**

The dead cells liberate their autolytic enzymes, and other enzymes (proteolytic) come from disintegrating polymorphs. There is an associated macrophage infiltration. These cells ingest particulate matter, either digesting or removing it.

**3. Ingrowth of granulation tissue**

This is characterized by proliferation of fibroblasts and an ingrowth of new blood vessels into the area of injury, with a variable number of inflammatory cells.

Fibroblasts actively synthesize and secrete extra-cellular matrix components, including fibronectin, proteoglycans, and collagen types I and III. The fibronectin and proteoglycans form the 'scaffolding' for rebuilding of the matrix. Fibronectin binds to fibrin and acts as a chemotactic factor for the recruitment of more fibroblasts and macrophages. The synthesis of collagen by fibroblasts begins within 24 hours of the injury although its deposition in the tissue is not apparent until 4 days. By day 5, collagen type III is the predominant matrix protein being produced; but by day 7 to 8, type I is prominent, and it eventually becomes the major collagen of mature scar tissue. This type I collagen is responsible for providing the tensile strength of the matrix in a scar. Coincident with fibroblast proliferation there is angiogenesis (neovascularization), a proliferation and formation of new small blood vessels. Vascular proliferation starts 48 to 72 hours after injury and lasts for several days.

With further healing, there is an increase in extracellular constituents, mostly collagen, with a decrease in the number of active fibroblasts and new vessels. Despite an increased collagenase activity in the wound (responsible for removal of built collagen), collagen accumulates at a steady rate, usually reaching a maximum 2 to 3 months after the injury. The tensile strength of the wound continues to increase many months after the collagen content has reached a maximum. As the collagen content of the wound increases, many of the newly formed vessels disappear. This vascular involution which takes place in a few weeks, dramatically transforms a richly vascularized tissue into a pale, avascular scar tissue.

**Wound contraction:**

Wound contraction is a mechanical reduction in the size of the defect. The wound is reduced approximately by 70-80% of its original size. Contraction results in much faster healing, since only one-quarter to one-third of the amount of destroyed tissue has to be replaced. If contraction is prevented, healing is slow and a large ugly scar is formed.

#### **IV. Molecular control of healing process**

As seen above, healing involves an orderly sequence of events which includes regeneration and migration of specialized cells, angiogenesis, proliferation of fibroblasts and related cells, matrix protein synthesis and finally cessation of these processes. These processes, at least in part, are mediated by a series of low molecular weight polypeptides referred to as growth factors.

**These growth factors have the capacity to stimulate cell division and proliferation.**

**Some of the factors, known to play a role in the healing process, are briefly discussed below.**

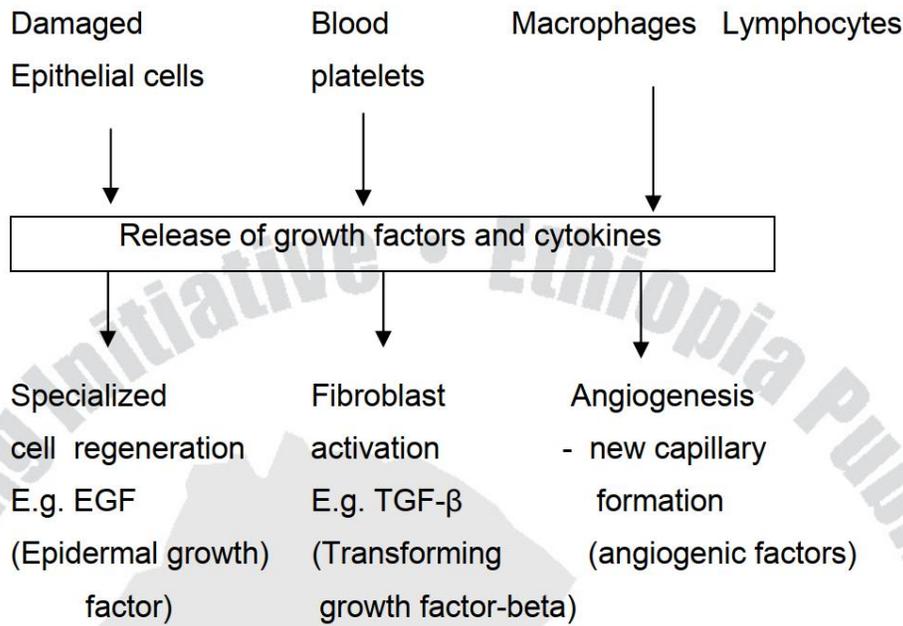
##### **Sources of Growth Factors:**

**Following injury, growth factors may be derived from a number of sources such as:**

1. Platelets, activated after endothelial damage,
2. Damaged epithelial cells,
3. Circulating serum growth factors,
4. Macrophages, or
5. Lymphocytes recruited to the area of injury

The healing process ceases when lost tissue has been replaced. The mechanisms regulating this process are not fully understood. TGF- $\beta$  acts as a growth inhibitor for both epithelial and endothelial cells and regulates their regeneration.

The summary of molecular control of the healing process is illustrated with the diagram shown below.



## VI. Wound Healing

The two processes of healing, described above, can occur during healing of a diseased organ or during healing of a wound. A wound can be accidental or surgical. Now, we will discuss skin wound healing to demonstrate the two basic processes of healing mentioned above.

Healing of a wound demonstrates both epithelial regeneration (healing of the epidermis) and repair by scarring (healing of the dermis).

**There are two patterns of wound healing depending on the amount of tissue damage:**

1. Healing by first intention (Primary union)
2. Healing by second intention

**These two patterns are essentially the same process varying only in amount.**

### **1. Healing by first intention (primary union)**

The least complicated example of wound healing is the healing of a clean surgical incision

(Fig. 4-4, left). The wound edges are approximated by surgical sutures, and healing occurs with a minimal loss of tissue. Such healing is referred to, surgically, as “primary union” or “healing by first intention”. The incision causes the death of a limited number of epithelial cells as well as of dermal adnexa and connective tissue cells; the incisional space is narrow and immediately fills with clotted blood, containing fibrin and blood cells; dehydration of the surface clot forms the well-known scab that covers the wound and seals it from the environment almost at once.

Within 24 hours, neutrophils appear at the margins of the incision, moving toward the fibrin clot. The epidermis at its cut edges thickens as a result of mitotic activity of basal cells and, within 24 to 48 hours, spurs of epithelial cells from the edges both migrate and grow along the cut margins of the dermis and beneath the surface scab to fuse in the midline, thus producing a continuous but thin epithelial layer. By day 3, the neutrophils have been largely replaced by macrophages. Granulation tissue progressively invades the incisional space. Collagen fibers are now present in the margins of the incision, but at first these are vertically oriented and do not bridge the incision. Epithelial cell proliferation continues, thickening the epidermal covering layer. By day 5, the incisional space is filled with granulation tissue. Neovascularization is maximal. Collagen fibrils become more abundant and begin to bridge the incision. The epidermis recovers its normal thickness and differentiation of surface cells yields a mature epidermal architecture with surface keratinization.

During the second week, there is continued accumulation of collagen and proliferation of fibroblasts. Leukocytic infiltrate, edema, and increased vascularity have largely disappeared. At this time, the long process of blanching begins, accomplished by the

increased accumulation of collagen within the incisional scar, accompanied by regression of vascular channels.

By the end of the first month, the scar comprises a cellular connective tissue devoid of inflammatory infiltrate, covered now by an intact epidermis. The dermal appendages that have been destroyed in the line of the 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.

## **2. Healing by second intention (secondary union)**

When there is more extensive loss of cells and tissue, such as occurs in infarction, inflammatory ulceration, abscess formation, and surface wounds that create large defects, the reparative process is more complicated. The common denominator in all these situations is a large tissue defect that must be filled. Regeneration of parenchymal cells cannot completely reconstitute the original architecture. Abundant granulation tissue grows in from the margin to complete the repair. This form of healing is referred to as “secondary union” or “healing by second intention.”

### **Secondary healing differs from primary healing in several respects:**

1. Inevitably, large tissue defects initially have more fibrin and more necrotic debris and exudate that must be removed. Consequently, the inflammatory reaction is more intense.
2. Much larger amounts of granulation tissue are formed. When a large defect occurs in deeper tissues, such as in a viscus, granulation tissue bears the full responsibility for its closure, because drainage to the surface cannot occur.
3. Perhaps the feature that most clearly differentiates primary from secondary healing is the phenomenon of wound contraction, which occurs in large surface wounds.
4. Healing by second intention takes much longer than when it occurs by first intention.

## **VI. Factors that influence wound healing**

A number of factors can alter the rate and efficiency of healing. These can be classified in to those which act locally, and those which have systemic effects. Most of these factors have been established in studies of skin wound healing but many are likely to be of relevance to healing at other sites.

### **Local Factors**

- **Type, size, and location of the wound**

A clean, aseptic wound produced by the surgeon's scalpel heals faster than a wound produced by blunt trauma, which exhibits abundant necrosis and irregular edges. Small blunt wounds heal faster than larger ones. Injuries in richly vascularized areas (e.g., the face) heal faster than those in poorly vascularized ones (e.g., the foot).

In areas where the skin adheres to bony surfaces, as in injuries over the tibia, wound contraction and adequate apposition of the edges are difficult. Hence, such wounds heal slowly.

- **Vascular supply**

Wounds with impaired blood supply heal slowly. For example, the healing of leg wounds in patients with varicose veins is prolonged. Ischemia due to pressure produces bed sores and then prevents their healing. Ischemia due to arterial obstruction, often in the lower extremities of diabetics, also prevents healing.

- **Infection**

Wounds provide a portal of entry for microorganisms. Infection delays or prevents healing, promotes the formation of excessive granulation tissue (proud flesh), and may result in large, deforming scars.

- **Movement**

Early motion, particularly before tensile strength has been established, subjects a wound to persistent trauma, thus preventing or retarding healing.

- **Ionizing radiation**

Prior irradiation leaves vascular lesions that interfere with blood supply and result in slow wound healing. Acutely, irradiation of a wound blocks cell proliferation, inhibits contraction, and retards the formation of granulation tissue.

### **Systemic Factors:**

#### **• Circulatory status**

Cardiovascular status, by determining the blood supply to the injured area, is important for wound healing. Poor healing attributed to old age is often due, largely, to impaired circulation.

#### **• Infection:**

Systemic infections delay wound healing.

#### **• Metabolic status**

Poorly controlled diabetes mellitus is associated with delayed wound healing. The risk of infection in clean wound approaches fivefold the risk in non- diabetics.

In diabetic patients, there can be impaired circulation secondary to arteriosclerosis and impaired sensation due to diabetic neuropathy. The impaired sensation renders the lower extremity blind to every day hazards. Hence, in diabetic patients, wounds heal the very slowly.

#### **• Nutritional deficiencies**

Protein deficiency, In protein depletion there is an impairment of granulation tissue and collagen formation, resulting in a great delay in wound healing.

Vitamin deficiency, Vitamin C is required for collagen synthesis and secretion. It is required in hydroxylation of proline and lysine in the process of collagen synthesis.

Vitamin C deficiency (scurvy) results in grossly deficient wound healing, with a lack of vascular proliferation and collagen deposition.

Trace element deficiency, Zinc (a co-factor of several enzymes) deficiency will retard healing by preventing cell proliferation. Zinc is necessary in several DNA and RNA

polymerases and transferases; hence, a deficiency state will inhibit mitosis. Proliferation of fibroblasts (fibroplasia) is, therefore, retarded.

- **Hormones**

Corticosteroids impair wound healing, an effect attributed to an inhibition of collagen synthesis. However, these hormones have many other effects, including anti-inflammatory actions and a general depression of protein synthesis. It also inhibits fibroplasia and neovascularization. Both epithelialization and contraction are impaired. It is, therefore, difficult to attribute their inhibition of wound healing to any one specific mechanism. Thyroid hormones, androgens, estrogens and growth hormone also influence wound healing. This effect, however, may be more due to their regulation of general metabolic status rather than to a specific modification of the healing process.

### Complications of Wound Healing

Abnormalities in any of the three basic healing processes – contraction, repair, and regeneration – result in the complications of wound healing

#### 1. Infection

A wound may provide the portal of entry for many organisms. Infection may delay healing, and if severe stop it completely.

#### 2. Deficient Scar Formation

Inadequate formation of granulation tissue or an inability to form a suitable extracellular matrix leads to deficient scar formation and its complications. The complications of deficient scar formation are:

a. Wound dehiscence & incisional hernias b. Ulceration

a. Wound Dehiscence and Incisional Hernias:

Dehiscence (bursting of a wound) is of most concern after abdominal surgery. If insufficient extracellular matrix is deposited or there is inadequate cross-linking of the matrix, weak scars result. Dehiscence occurs in 0.5% to 5% of abdominal operations. Inappropriate suture material and poor surgical techniques are important factors. Wound infection, increased mechanical stress on the wound from vomiting, coughing, or ileus is a factor in most cases of abdominal dehiscence. Systemic factors that predispose to dehiscence include poor metabolic status, such as vitamin C deficiency, hypoproteinemia, and the general inanition that often accompanies metastatic cancer. Dehiscence of an abdominal wound can be a life-threatening complication, in some studies carrying a mortality as high as 30%.

An incisional hernia, usually of the abdominal wall, refers to a defect caused by poor wound healing following surgery into which the intestines protrude.

b. Ulceration:

Wounds ulcerate because of an inadequate intrinsic blood supply or insufficient vascularization during healing. For example, leg wounds in persons with varicose veins or severe atherosclerosis typically ulcerate. Nonhealing wounds also develop in areas devoid of sensation because of persistent trauma. Such trophic or neuropathic ulcers are occasionally seen in patients with leprosy, diabetic peripheral neuropathy and in tertiary syphilis from spinal involvement (in tabes dorsalis).

### 3. Excessive Scar Formation

An excessive deposition of extracellular matrix at the wound site results in a hypertrophic scar or a keloid (See Figure 4-5 and 4-6). The rate of collagen synthesis,

the ratio of type III to type I collagen, and the number of reducible cross-links remain high, a situation that indicates a “maturation arrest”, or block, in the healing process.

### **Structure of bone:**

Bone is composed of calcified osteoid tissue, which consists of collagen fibers embedded in a mucoprotein matrix (osteomucin). Depending on the arrangement of the collagen fibers, there are two histological types of bone:

#### **1. Woven, immature or non-lamellar bone**

This shows irregularity in the arrangement of the collagen bundles and in the distribution of the osteocytes. The osseomucin is less abundant and it also contains less calcium.

#### **2. Lamellar or adult bone**

In this type of bone, the collagen bundles are arranged in parallel sheets.

### **Stages in Fracture Healing (Bone Regeneration)**

Stage 1: Haematoma formation. Immediately following the injury, there is a variable amount of bleeding from torn vessels; if the periosteum is torn, this blood may extend into the surrounding muscles. If it is subsequently organized and ossified, myositis ossificans results.

Stage 2: Inflammation. The tissue damage excites an inflammatory response, the exudate adding more fibrin to the clot already present. The inflammatory changes differ in no way from those seen in other inflamed tissues. There is an increased blood flow and a polymorphonuclear leucocytic infiltration. The haematoma attains a fusiform shape.

Stage 3: Demolition. Macrophages invade the clot and remove the fibrin, red cells, the inflammatory exudate, and debris. Any fragments of bone, which have become detached from their blood supply, undergo necrosis, and are attacked by macrophages and osteoclasts.

Stage 4: Formation of granulation tissue. Following this phase of demolition, there is an ingrowth of capillary loops and mesenchymal cells derived from the periosteum and the endosteum of the cancellous bone. These cells have osteogenic potential and together with the newly formed blood vessels contribute to the granulation – tissue formation.

Stage 5: Woven bone and cartilage formation. The mesenchymal “osteoblasts” next differentiate to form either woven bone or cartilage. The term “callus”, derived from the Latin and meaning hard, is often used to describe the material uniting the fracture ends regardless of its consistency. When this is granulation tissue, the “callus” is soft, but as bone or cartilage formation occurs, it becomes hard.

Stage 6: Formation of lamellar bone. The dead calcified cartilage or woven bone is next invaded by capillaries headed by osteoclasts. As the initial scaffolding (“provisional callus”) is removed, osteoblasts lay down osteoid, which calcifies to form bone. Its collagen bundles are now arranged in orderly lamellar fashion, for the most part concentrically around the blood vessels, and in this way the Haversian systems are formed. Adjacent to the periosteum and endosteum the lamellae are parallel to the surface as in the normal bone. This phase of formation of definitive lamellar bone merges with the last stage.

Stage 7: Remodeling. The final remodeling process involving the continued osteoclastic removal and osteoblastic laying down of bone results in the formation of a bone, which differs remarkably little from the original tissue. The external callus is slowly removed, the intermediate callus becomes converted into compact bone containing Haversian systems, while the internal callus is hollowed out into a marrow cavity in which only a few spicules of cancellous bone remain.