HEALING/ REPAIR

I. OVERVIEW: WHAT HAPPENS WHEN CELLS ARE INJURED OR DIE

A. POSSIBLE OUTCOMES

1. Adaptation
2. Resolution/Repair (Healing)
3. Death of the organism

II. REPAIR

A. In the face of injury, the body seeks to maintain normal structure and function. Healing of injured cells begins with inflammation and ends with repair.

B. REPAIR: Repair is the process by which damaged or dead tissue is replaced by normal issue. The damaged tissue may consist of only parenchymal cells (the functional tissue of an organ) or a combination of cells and the connective tissue framework of an organ. Mechanisms of repair involve the migration, proliferation and differentiation of cells as well as an interaction of cells with the extracellular matrix (network of interstitial proteins).

1. **Regeneration** is the reparative process by which injured or dead cells are replaced by replicating cells of the same type. It is assumed that the connective tissue framework (extracellular matrix) of the organ is intact and serves as “scaffolding” for the orderly replacement of parenchymal cells. (Example: mild viral hepatitis).

2. **Replacement by connective tissue** refers to scar formation: This is a reparative process by which a defect in tissue is replaced by connective tissue. The defect in the organ involves either
   a. Destruction of the connective tissue framework along with parenchymal cells. (example: lung abscess)
   b. Parenchymal cells which can not regenerate. (example: necrosis of myocardium).

3. Regeneration and replacement by connective tissue often occur simultaneously in the repair of a diseased organ because parenchymal cells and extracellular matrix have been destroyed. (example: skin laceration).
III. REPAIR: REGENERATION

A. Classification of cells is based on their ability to regenerate. The growth of cells is the result of complex molecular reactions which reflect a balance between stimulating and inhibiting chemical signals. All normal cells may be grouped into three categories based on their ability to respond to growth stimulation and to regenerate:

1. Labile cells: Continuously divide. Examples: Epithelium of skin and mucous membranes; hematopoietic cells.
2. Stable cells: Low level of replication but rapidly divide when stimulated. Example: Parenchymal cells of the liver and kidney; fibroblasts, smooth muscle cells, endothelium.
3. Permanent cells: Non-dividing Examples: cardiac muscle, skeletal muscle

B. PHASES OF THE CELL CYCLE

IV. REPAIR: REPLACEMENT BY CONNECTIVE TISSUE

A. COMPONENTS OF PROCESS

1. Angiogenesis- Formation of new blood vessels. (Refer to Figure 3-25 in “Robbins Basic Pathology”)
   Important mediator: Vascular endothelial growth factor (VEGF)
2. Migration and proliferation of fibroblasts. Important mediators: Transforming growth factor β (TGF-β), Platelet derived growth factor (PDGF), Fibroblast growth factor (FGF)
3. Formation and deposition of extracellular matrix (by fibroblasts).
4. Maturation and organization (remodeling) of the fibrous tissue elements.

GRANULATION TISSUE

1. Definition: Granulation tissue is specialized tissue that fills in defects within organs when non-regenerative cells and/or connective tissue framework is destroyed during a disease process. Granulation tissue consists of proliferating fibroblasts laying down immature connective tissue elements and proliferating (new) blood vessels. The tissue appears red and edematous to the naked eye. It is only present during healing or an attempt to heal destroyed tissue. Process of transforming granulation tissue into dense scar. With time, granulation tissue changes as the connective tissue elements, such as collagen, mature, and blood vessels become less prominent.

B. CLINICAL MODEL OF REPAIR (HEALING): WOUND REPAIR

1. Steps in healing of a skin laceration:
   a. Injury produces a defect in skin and incites an inflammatory reaction.
   b. Blood clot (fibrin and fibronectin).
   c. Epithelium regenerates and migrates to cover the defect.
   d. Cells (fibroblasts, myofibroblasts, macrophages) proliferate and migrate into the defect (filled with clot). Macrophages remove debris, such as dead cells, and secrete cytokines. Fibroblasts, under chemical mediation, produce extracellular connective tissue matrix. Myofibroblasts contact the wound.
   e. Simultaneously, capillaries (endothelium) at the edge of the defect proliferate and extend into the defect under the influence of chemical mediation.
   f. Over time (weeks to months) the defect filled with granulation tissue becomes remodeled into mature collagen (scar) and parenchymal cells. The wound acquires strength through this process (vitamin C required).

2. Healing by first intention (primary union): The skin wound is generally clean and seen by a physician within a few hours of the injury. Likewise, the defect is generally limited in the amount destroyed tissue. The physician decreases the size of the defect by closing the gap with sutures, following cleansing and debridement. The maneuvers allow for the healing process to proceed rapidly
and without complications. Although weeks to months may pass before the healing process is complete, sutures will usually be removed after 5-10 days, depending on the anatomical site.

3. Healing by second intention (secondary union): Generally, when a skin wound is large (extensive destruction) or severely contaminated or infected (patient presents for treatment days after the injury), it is allowed to heal by secondary intention. The wound is allowed to “granulate in” without closing the gap with sutures, following debridement and cleansing. Although the process of healing is the same, it takes longer because of the size of the defect. The same process of healing occurs in an internal organ when there is extensive destruction of tissue.

C. FACTORS WHICH INFLUENCE INFLAMMATION AND REPAIR (HEALING): GENERAL PRINCIPLES

1. Local Factors
   b. Vascular supply: Inflammation and healing can take place only when there is an adequate blood supply. Devitalized tissue will not heal. Tissue with poor vascularity may heal with difficulty or be more prone to infection (example: abscess, fat).
   c. Infection: The presence of bacteria will continue to incite an inflammatory reaction, preventing or prolonging healing.
   d. Foreign bodies: A foreign substance (splinter, suture) will intensify inflammation and prevent healing when bacteria are present.
   e. Ionizing Radiation: Radiation decreases the vascular supply to tissue.

2. Systemic Factors
   a. Circulation: Poor circulation as seen in congestive heart failure or severe atherosclerosis impairs the transportation of oxygen, inflammatory cells and chemical mediators to the site of injury.
   b. Infection: systemic infection may overwhelm the immune system.
   Nutrition: vital substances necessary for healing - may not be available in a state of poor nutrition examples: proteins; vitamin C which is essential for collagen cross-linking; copper which is a cofactor for lysyl
oxidase which cross-links lysine and hydroxylysine to form stable collagen; zinc which is a cofactor for collagenase

c. Hormones: steroids inhibit the inflammatory process, impairing healing (example; steroid medication, Cushing’s syndrome).

D. COMPLICATION OF WOUND HEALING

Defective scar formation: wound dehiscence (rupture of wound), incisional hernia.

I. Excessive scar formation:
   a. Hypertrophic scar – Excess production of scar tissue localized to the wound; may regress
   b. Keloid – Accumulation of exuberant amount of collagen; grows beyond wound boundaries. May be hereditary, more common in African Americans

2. Dehiscence
   Opening of healing or partially healed wound with separation of its edge
   Can be result of: mechanical factors; infection; ischemic necrosis of sutured edges

Practice Question

A 26-year-old riding a motor cycle hits a tree. He incurs blunt force abdominal trauma. In response to this injury, cells in tissues of the abdomen are stimulated to enter the G1 phase of the cell cycle from the G0 phase. Which of the following cell types is most likely to remain in G0 following this injury?

A Smooth muscle
B Endothelium
C Skeletal muscle
D Fibroblast
E Hepatocyte

Answer C