WOUND-HEALING PROCESS

Inflammation

Whenever tissues are injured or destroyed, the adjacent cells respond to repair them. An immediate response to any injury is the inflammatory reaction. Soon after constriction of capillaries (which stops blood leakage), dilation occurs. At the same time there is a great increase of activities in the endothelial cells lining the capillaries. The capillaries will be covered by adjacent leukocytes, erythrocytes, and platelets. Concurrently with vasodilation, leakage of plasma from capillaries occurs. This fluid combined with the migrating leukocytes and dead tissues will constitute exudate. Once enough cells (see Table 7-1 for definitions of cells) are accumulated by lysis, the exudate becomes pus. It is important to know that pus can sometimes occur in nonbacterial inflammation. At the time of damage to the capillaries, the local lymphatics are also damaged since the latter are more fragile than the capillaries. However, the leakage of fluids from the capillaries will provide fibrinogen and other formed elements of the blood clotting system which will quickly plug the damaged lymphatics, thus localizing the inflammatory reaction. All of the reactions mentioned above-vasodilation of capillaries, leakage of fluid into the extravascular space, and plugging of lymphatics-will provide the classic inflammatory signs: redness, swelling, and heat which can lead to local pain. When the tissue injury is extensive or the wound contains either irritants or bacteria, the inflammation may lead to extensive tissue destruction. Collagenase, a proteolytic enzyme capable of digesting collagen, (1) carries out the tissue destruction. The enzyme is released from granulocytes which in turn are lysed by the lower pH at the wound site. Local pH can drop to below 5.2 at the injured site from normal values of 7.4-7.6. If there is no drainage for the necrotic debris, lysed granulocytes, formed blood elements, etc., then the site becomes a severely destructive inflammation resulting in a necrotic abscess. If the severe inflammation persists without the healing process occurring within 3-5 days, a chronic inflammatory process commences. This is marked by the presence of mononuclear cells called macrophages which can coalesce to form multinucleated giant cells (Figure 7-1). The macrophages are phagocytic and remove foreign material or bacteria. Sometimes the mononuclear cells evolve into histiocytes which regenerate collagen. This regenerated collagen is used to unite the wound or wall-off unremovable foreign materials by encapsulation.

In a chronic inflammatory reaction, lymphocytes occur as clumps or foci. These cells are the primary source of immunogenic agents which become active if foreign proteins are not removed by the body's primary defence. An autoimmune reaction is suggested as a foreign body reaction of nonproteinaceous materials like silica.

Cellular Response to Repair

Soon after injury, the mesenchymal cells evolve into migratory fibroblasts which move into the injured site while the necrotic debris, blood clots, etc. are removed by the granulocytes and macrophages. The inflammatory exudate contains fibrinogen which is converted into

fibrin by enzymes released through blood and tissue cells (see Section 7.3). The fibrin scaffolds the injured site. The migrating fibroblasts use the fibrin scaffolds as a

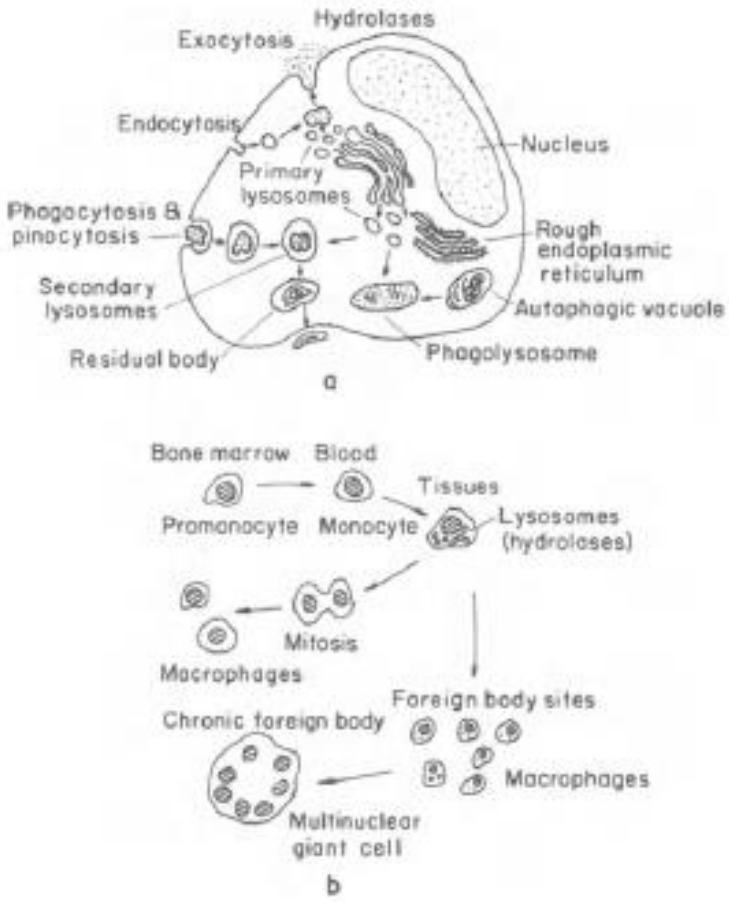

Figure 7-1. (a) The activated macrophage and (b) development of the multinuclear foreign body giant cell. (From Ref. 8.)

framework onto which collagen is deposited. New capillaries are formed following the migration of fibroblasts; then the fibrin scaffolds are removed by the fibrinolytic enzymes activated by the endothelial cells. The endothelial cells together with the fibroblasts liberate collagenase which limits the collagen content of the wound. After 2-4 weeks of fibroblastic activities the wound undergoes remodelling by decreasing the glycoprotein and

polysaccharide content of the scar tissue and lowering the number of synthesizing fibroblasts. A new balance of collagen synthesis and dissolution is reached and the maturation phase of the wound begins. The time required for the wound-healing process varies with various tissues although the basic steps described here can be applied to all connective tissue wound-healing processes.

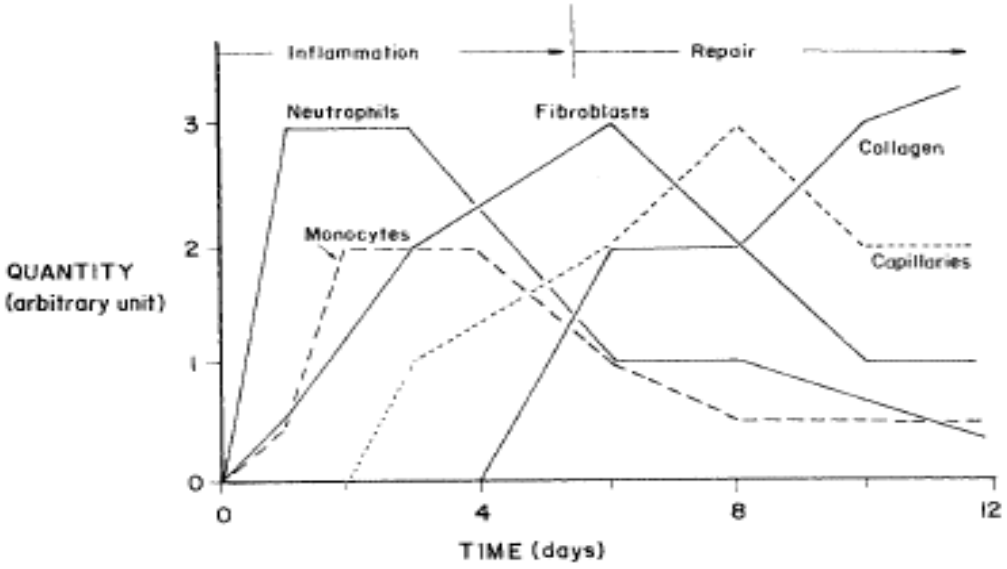

Figure 7-2. Soft tissue wound-healing sequence. (From Ref. 2.)

The healing of soft tissues, especially that of the skin wound, has been studied intensively since this is germane to all surgery. The degree of healing can be determined by histochemical or physical parameters. A combined method will give a better understanding of the overall healing process. Figure 7-2 is a schematic diagram of sequential events of the cellular response of soft tissues. The tensile strength of the wound is not proportional to the amount of collagen deposited in the injured site as shown in Figure 7-3. This indicates that there is a latent period for the collagen molecules (procollagen is deposited by fibroblasts) to polymerize. It may take additional time to align the fibers in the direction of stress and cross-link fibrils in order to increase the physical strength closer to a normal level. This collagen restructuring process requires more than 6 months to complete although the wound strength never reaches the original value. The wound strength can be affected by many variables, that is, nutrition, temperature, presence of other wounds, and oxygen tension. Other factors such as drugs, hormones, irradiation, and electrical stimulation all affect the normal wound-healing process. The healing of bone fractures is regenerative rather than simple repair as seen in other tissues except liver. However, the extent of regeneration is limited in humans. The cellular events following fracture of bone are illustrated in Figure 7-4. When a bone is fractured, many blood vessels (including the adjacent soft tissues) hemorrhage and form a blood clot.

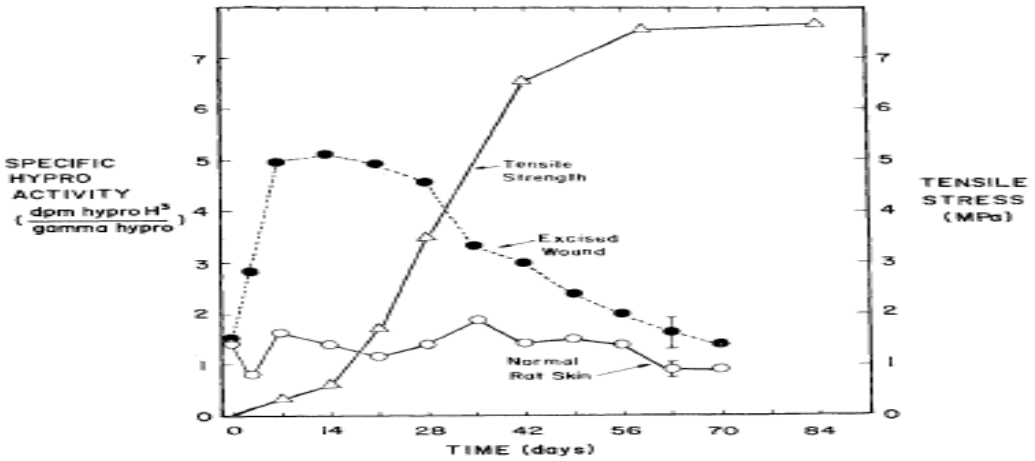

Figure 7-3. Tensile strength and rate of collagen synthesis of rat skin wounds. (From Ref. 3.)

around the fracture site. As in any wound repair, shortly after fracture the fibroblasts and osteogenic cells in the outer layer of the periosteum migrate and proliferate toward the injured site. These cells lay down a fibrous collagen matrix for callus formation. Osteoblasts evolve from the osteogenic cells near the bone surface to calcify the callus into trabeculae, forming a spongy bone. The osteogenic cells which migrate further away from an established blood supply become chondroblasts which lay down cartilage. Thus, after about 2-4 weeks the periosteal callus is made up of three parts as shown in Figure 7-5. Simultaneously with the external callus formation a similar repair process occurs in the marrow cavity. Since there is an abundant supply of blood, the cavity turns into callus rather quickly and becomes fibrous or spongy bone.

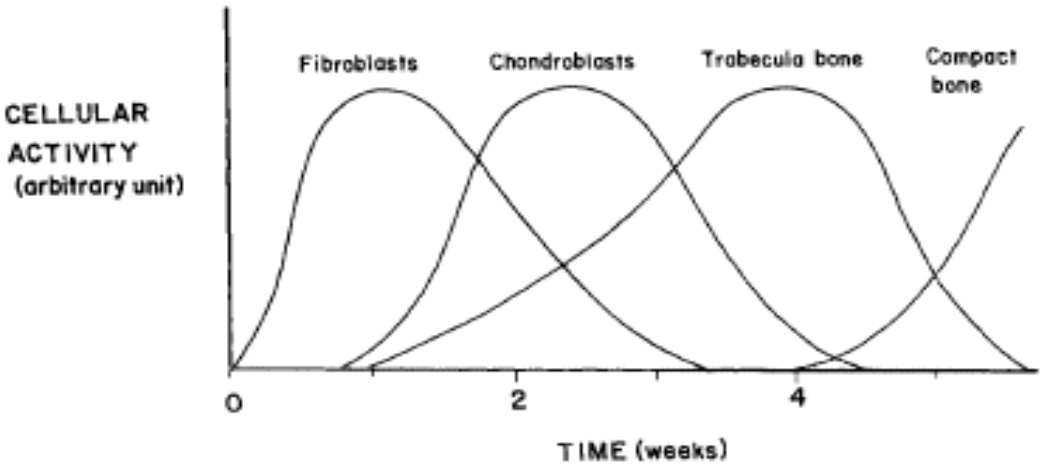

Figure 7-4. Sequence of events following bone fracture. (From Ref. 4.)

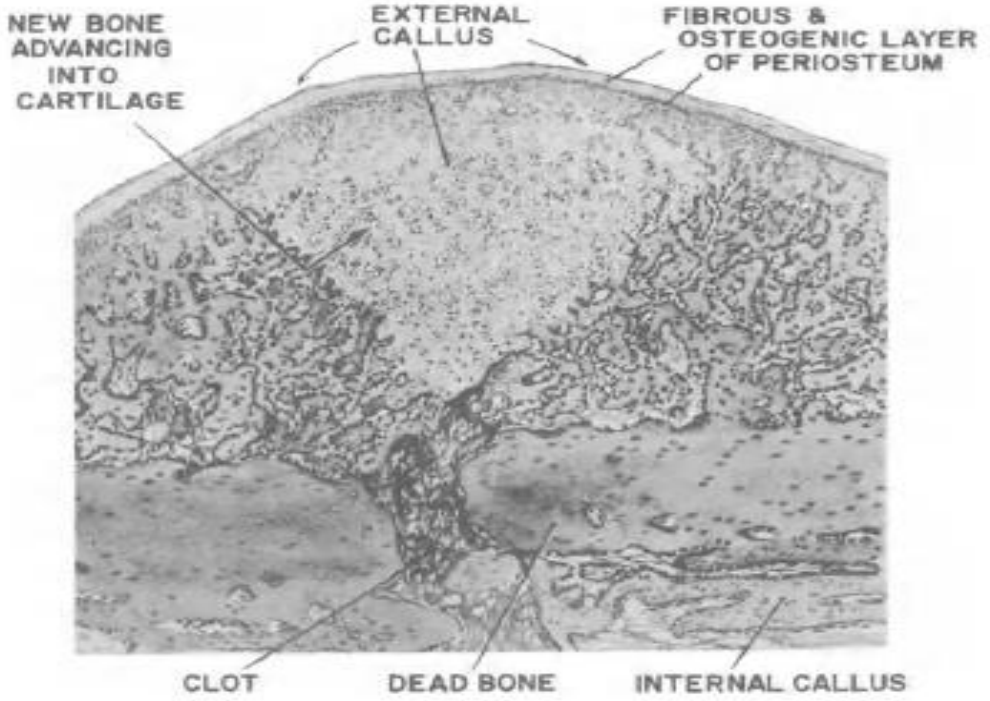

Figure 7-5. A drawing of a longitudinal section of fractured rib of a rabbit after 2 weeks, H & E stain. (From Ref. 5.)

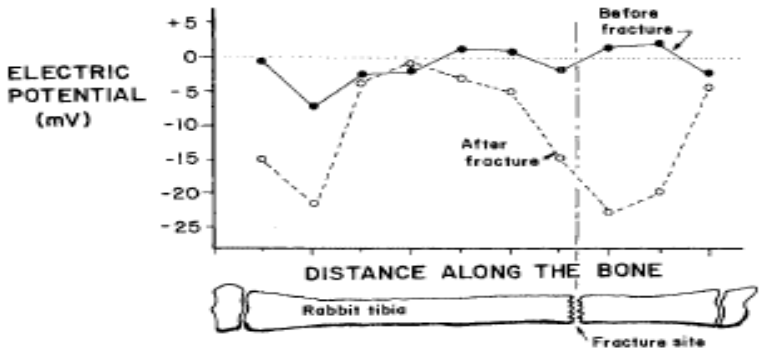

Figure 7-6. Skin surface of rabbit limb before and after fracture. Note that the fracture site has increased electronegative potential. (From Ref. 6.)

New trabeculae develop in the fracture site by appositional growth and the spongy bone turns into compact bone. This maturation process begins after about 4 weeks. Some other interesting observations have been made on the healing of bone fractures in relation to the synthesis of polysaccharides on collagen. It is believed that the amount of collagen and polysaccharides is closely related to the cellular events following fracture. When the amount of collagen starts to increase, it marks the onset of the remodeling process. This occurs after about 1 week. Another interesting observation is the electrical potential (or biopotential) measured in the long bone before and after fracture as shown in Figure 7-6. The high electronegativity in the vicinity of the fracture marks an increased cellular activity in the

tissues. Thus, there is a maximum negative potential in the epiphysis in the normal bone since this zone is the site of greatest activity (the growth plate is in the epiphysis).