THE PRINCIPLES OF WOUND HEALING

CHAPTER 1

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1. What events occur during each of the primary phases of wound healing?

Wound healing has three principal phases: inflammatory, proliferative, and remodeling. The **inflammatory phase** begins at the time of injury and lasts for 24 to 48 hours. This phase begins with hemostasis and leads to inflammation. Platelets form the initial thrombus release growth factors that induce the chemotaxis and proliferation of neutrophils and macrophages, which cooperate to remove necrotic tissue, debris, and bacteria from the wound. Macrophages then become the prominent cell of this phase and release various growth factors and cytokines that change the relatively acellular wound into a highly cellular environment. Next, fibroblasts proliferate to become the dominant cell of the **proliferative phase.** They produce collagen, which provides structure to the wound and replaces the fibronectin–fibrin matrix. Angiogenesis of new capillaries occurs to sustain the fibroblast proliferation. Keratinocytes also epithelialize the wound. The **remodeling phase** begins at about 2 to 3 weeks and can last up to 2 years. At this time, collagen synthesis and degradation reach equilibrium. Fibroblasts organize and cross-link the collagen, wound strength gradually increases, wound contraction occurs, and the wound loses its pink or purple color as capillary and fibroblast density decrease. All stages may vary in length because of infection, malnutrition, or other exogenous factors.

2. What roles do platelet-derived growth factor and transforming growth factor beta play in wound healing?

Platelet-derived growth factor (PDGF) is released initially by platelets in the inflammatory phase during the formation of the initial thrombus. It is an important chemoattractant and activator of macrophages, which arrive to orchestrate wound healing. These macrophages then secrete additional growth factors that include more PDGF. These growth factors attract, recruit, and activate additional macrophages.

Transforming growth factor beta (TGF-β) is released by macrophages and platelets. It is a potent chemoattractant and activator of fibroblasts, stimulating them to form collagen. TGF-β is the major growth factor involved in collagen synthesis.

3. What role do macrophages play in wound healing?

Macrophages play a critical role in the inflammatory phase. They help to débride the wound through phagocytosis, but, more importantly, they are the primary source of proinflammatory cytokines and growth factors such as the interleukins (IL-1, IL-6, IL-8), PDGF, TGF-β, epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF). These humoral factors stimulate the recruitment, activation, and proliferation of additional macrophages, lymphocytes, fibroblasts, and endothelial cells. These cytokines also act in an autocrine fashion to tremendously amplify their expression.

4. Are neutrophils essential for strengthening wounds?

Neutrophils remove necrotic debris and bacteria from the wound initially during the inflammatory phase of wound healing but play no role in strengthening the wound. Unlike macrophages, neutrophils are not a source of growth factors in a healing wound.

5. How does the wound's collagen composition compare between the early and late stages of wound healing?

Type I collagen is the most abundant type of collagen in normal dermis (approximately 80% to 90%). During the early stages of wound healing, fibroblasts actively produce type III collagen, which may account for 30% of the collagen in a healing wound. By week 2, type I collagen again becomes the principal collagen produced by fibroblasts. During remodeling, type III collagen is replaced by type I collagen to restore the normal dermal collagen composition.

6. When does collagen production peak in a healing wound?

Net collagen accumulation peaks after 2 to 3 weeks after injury. Collagen production peaks after 6 weeks but is balanced by collagen degradation. Although no net increase in collagen occurs during remodeling, collagen synthesis and degradation continue at elevated rates for up to 1 year after the initial injury.

7. During remodeling, no net increase in collagen occurs but wound tensile strength increases greatly. Why?

Initial wound healing is notable for production of large amounts of randomly oriented collagen. During remodeling, this collagen becomes cross-linked and replaced with more organized collagen that is better arranged to resist mechanical stress. Like raw wool being woven into strong yarn, the remodeled collagen is compacted into fibers that are many times stronger than random collagen fibrils. However, the final strength of the new collagen never reaches the strength of uninjured collagen.

8. What is the rationale for not allowing patients with hernias to do sit-ups for 6 weeks after a herniorrhaphy?

Wound tensile strength initially is relatively weak. It increases slowly for about 2 weeks and then increases rapidly for 4 weeks in a linear fashion. By 6 weeks after injury, the wound has gained about 50% of its ultimate strength and is strong enough to tolerate moderate forces. In the elderly, it may be prudent to be more patient because gains in tensile strength are slower.

9. A well-healed wound eventually reaches what percentage of prewound strength?

Classic studies by Levenson et al. in 1965, using a rat model, demonstrated that wounds never achieve more than 80% of normal prewound tensile strength.

10. What is the wound healing defect in Ehlers-Danlos syndromes?

Ehlers-Danlos syndromes (EDS) are a heterogeneous group of connective tissue disorders characterized by hypermobile joints, hyperextensible skin, and generalized fragility of connective tissues. They are associated with defects in the synthesis, cross-linking, or structure of collagen that can lead to decreased wound strength and delays in wound healing. Patients are prone to wound dehiscence, which forms broad, thin, shiny scars resembling cigarette paper.

11. What is the mechanism of wound contraction?

Fibroblasts in contracting wounds have increased actin microfilaments and are designated as myofibroblasts. These myofibroblasts orient themselves along lines of tension and pull collagen fibers together. Wound contraction is part of the normal healing process that closes wounds to the external environment. Scar contracture is an abnormal shortening and thickening of a scar that may cause functional (if across a joint) and/or cosmetic deformities.

12. By what three methods can wound healing be achieved?

A wound can heal through **primary intention** in the acute, clean surgical wound. This relatively rapid process involves manual approximation of the wound edges by suture, staples, or adhesive material. In **secondary intention,** a wound is allowed to heal through the physiologic processes of granulation and reepithelialization. This method leads to a relatively slow healing process and is used in chronic wounds that are more likely to be infected. In **tertiary intention,** healing occurs when primary closure is delayed, allowing the wound to granulate for a short period before closure through manual reapproximation or another technique. This method can be used to débride an infected, acute wound before closure. This is also designated *delayed primary closure.*

13. What is contact inhibition and how does it relate to epithelialization?

Contact inhibition is the concept that physical contact halts cell migration. Epithelial cells exhibit contact inhibition. They continue to proliferate and migrate across the surface of a wound until they contact each other, forming a continuous, single-layer sheet.

14. How long should a wound be kept dry after closing a surgical incision?

Well-approximated surgical incisions usually are epithelialized in 24 to 48 hours, forming a fluid barrier. Washing a wound once it is epithelialized to remove dried, crusted blood and exudates can reduce bacterial loads and culture media that could delay wound healing. For example, the benefits of washing and removing dried blood from a facial laceration far outweigh any risks to the wound. However, elderly patients epithelialize slower, so their wounds should be kept dry longer, particularly less well-vascularized areas such as lower extremities. If foreign material such a prosthetic joint is beneath an incision, it may be desirable to keep it dry for much longer to prevent potential contamination of the prosthesis.

15. Why do partial-thickness wounds reepithelialize faster than full-thickness wounds?

Epithelial cells are located not only in the epidermis but also in dermal sweat glands and hair follicles. In partial-thickness wounds, some epithelial islands and these dermal structures are preserved, so epithelial cell migration and proliferation from these remaining dermal appendages, sweat glands, and hair follicles all contribute to faster epithelialization. In full-thickness wounds, the entire dermis is destroyed, so epithelialization can only occur from the outer margins of the wound.

16. You are about to remove an actinic/seborrheic keratosis from a patient's face when he asks if there will be any scarring. How do you respond?

Actinic and seborrheic keratoses are limited to the epidermis. Scarring occurs following injury to the dermis. Injuries to the epidermis can heal without scarring, but if wound closure is delayed or deeper layers are injured, scarring results. Therefore, superficial skin lesions such as actinic/seborrheic keratoses can be removed without scarring if care is taken not to injure the deeper dermis.

17. After giving birth to her first baby, a patient asks if any treatments are available for stretch marks (striae distensae). What causes stretch marks? Are they amenable to treatment?

Stretch marks form when dermal collagen fibers are stretched and disrupted but the epidermis remains intact. The dermis forms a scar that is visible through the translucent epidermis. Because stretch marks are scars in the dermis, treatment involves scar excision or tissue destruction.

18. What techniques can be used to optimize healing of surgical wounds?

Any technique that reduces inflammation, minimizes tissue destruction, clears debris, and promotes a moist environment will optimize healing of surgical wounds. Some specific techniques are to perform meticulous hemostasis, limit the use of electrocautery, handle tissue with atraumatic instruments, achieve early and precise tissue approximation, avoid crush injury, and minimize suture material (foreign bodies) in the wound. Early and frequent cleansing helps to gently débride wounds by clearing surface exudates, bacteria, and debris. Also, evidence indicates that covering immature epithelium with silicone sheeting, paper tape, or other materials that simulate a mature stratum corneum can beneficially modulate the scarring process.

19. Is a wound less likely to spread if it is closed with intradermal polyglactic acid suture (Dexon, Vicryl) versus a nylon suture that is removed in 7 days?

Wounds can spread if closed under tension or if exposed to stretching forces. In the first 3 weeks of wound healing, the strength of a wound is only a small fraction of its eventual strength. Sutures removed or degraded before this time have little effect in preventing wound spreading. Polyglactic acid suture loses strength after 3 weeks, at which time the wound is still relatively weak. These results are similar to removing a nylon suture from the wound in 1 week. Leaving a permanent intradermal suture in place for several months has been shown to decrease spreading, and it is possible that a synthetic suture that retains strength for 6 to 8 weeks may have the same effect.

20. What is the ideal dressing?

In general, the ideal dressing should be simple, inexpensive, highly absorptive, and nonadherent. It should provide a moist environment for healing and should have antibacterial properties. However, wounds are not all the same; therefore, dressings should be selected such that their desirable properties (absorptive, antibacterial, etc.) fit the needs of the particular wound. Hundreds of dressings with various desirable properties are available on the market; however, none of them has been proven superior to gauze.

21. What are the benefits of occlusive dressings?

Occlusive dressings (e.g., polyurethane) maintain moist environments that promote faster reepithelialization than occurs under dry conditions. It has been shown that epithelialization under scabs does not occur as quickly as under moist dressings. When occlusive dressings are used, care should be taken to monitor for infection because the moist environment under the dressing makes an excellent medium for bacterial growth.

22. Which vitamins and minerals affect wound healing?

Vitamin A decreases the inflammation in wounds and may improve wound healing in steroid-dependent patients. Vitamin C is necessary for the hydroxylation of lysine and proline in collagen cross-linking. Essential fatty acids are required for all new cell synthesis. Magnesium and zinc are important cofactors for DNA synthesis, protein synthesis, and cellular proliferation. Copper-based enzymes catalyze the cross-linking of collagen and strengthen the collagen framework. These vitamins and minerals should be supplemented to prevent deficiency states; however, oversupplementation in the adequately nourished patient has not been shown to accelerate wound healing and, instead, may be deleterious.

23. Are there any specific products that help accelerate wound healing?

The Food and Drug Administration (FDA) has approved the use of PDGF for accelerating the healing of clean, well-vascularized, diabetic forefoot ulcers. Apligraf is a synthetic dermis that the FDA has approved for improving the treatment of refractory venous ulcers.

24. What is the wound vacuum-assisted closure, and how does it accelerate wound healing?

The wound vacuum-assisted closure (VAC) is a very useful occlusive dressing that provides a constant negative pressure to the wound bed. This negative pressure reduces tissue edema, removes exudates, lowers the bacterial burden, aids in tissue contraction, and may improve blood supply. This device has allowed many wounds requiring complex

reconstruction to heal with simpler options; however, it may be subject to overuse. It has applications for many acute and chronic wounds and has resulted in simpler solutions, such as skin grafts rather than complex flaps for successful wound closure.

25. You are reluctant to débride a decubitus ulcer with necrotic tissue in a chronically ill patient who has multiple medical problems and a coagulopathy. What are the alternatives to surgical débridement?

Several options are available. Topical creams that break down necrotic tissue can be applied to the wound. Commonly used agents include autolytic and enzymatic débridement creams. Autolytic débridement agents work by activating endogenous collagenases within the open wound to remove necrotic tissue. Enzymatic débridement agents are concentrated collagenases that directly digest the nonviable tissue.

26. What is a chronic wound?

Chronic wounds are those that fail to close in 3 months. They fall into three broad categories: diabetic ulcers, pressure ulcers, and ulcers secondary to venous hypertension. With meticulous wound care, most chronic wounds will close without surgical intervention.

27. What factors impair wound healing?

Although many factors influence wound healing in surgical patients, the most important are nutritional deficiencies (albumin <2.5 gm/dL), vitamin deficiencies (unusual), aging, wound infections, hypoxia, edema, steroids, diabetes, and radiation.

28. What effect does radiation have on wound healing?

Radiation damages endothelial cells, capillaries, and arterioles. This results in progressive loss of blood vessel volume and diminishes tissue perfusion in the affected area. Radiated fibroblasts show decreased proliferation and collagen synthesis, leading to diminished deposition of extracellular matrix. Lymphatics are likewise damaged, causing edema and poor clearance of infection in healing tissues.

29. Why does edema impair wound healing?

In normal tissue, each cell is only a few cell diameters away from the nearest capillary and receives oxygen and nutrients by diffusion. Edema impairs wound healing through several mechanisms. First, the additional extracellular water increases diffusion distances, resulting in lower tissue pO_2. Second, chronic edema may result in protein deposition in the extracellular matrix, which can act as a diffusion barrier for growth factors and nutrients, making them less available to cells. Finally, growth factors and nutrients are relatively diluted in the edematous fluid.

30. What factors are responsible for local wound ischemia?

Smoking, radiation, edema, diabetes, atherosclerosis, venous stasis, vasculitis, or prolonged pressure can affect the perfusion and oxygenation of a wound and cause local wound ischemia.

31. Is there a role for hyperbaric oxygen in wound healing?

Recent evidence suggests that oxygen serves not only as a necessary component in aerobic metabolism but as a signaling molecule for growth factor production. Based on the success of a number of retrospective studies, the use of hyperbaric oxygen to increase tissue oxygenation has become widespread, particularly in patients with diabetic foot ulcers. However, large, prospective, randomized trials have not been conducted.

32. What is the definition of wound infection?

It is the product of the entrance, growth, metabolic activities, and resultant pathophysiologic effects of microorganisms in the tissues. A wound with bacterial counts greater than 10^5 organisms per gram of tissue is considered infected and unlikely to heal without further treatment.

33. What causes hypertrophic/keloid scars? What features distinguish them?

Hypertrophic/keloid scars are believed to be due to an excessive inflammatory response during wound healing. Keloids usually extend beyond the boundaries of the original tissue injury and become progressively larger. They act similar to benign tumors and may extend into surrounding tissue. Hypertrophic scars are elevated but do not extend outside the original borders of the wound. Keloids are more common in people with dark complexions. Hypertrophic scarring occurs more often in Asian and African skin. Keloid scarring is transmitted in an autosomal dominant pattern in some patients. Both conditions are remarkable for overproduction of all components of the extracellular matrix, but absolute numbers of fibroblasts are not increased.

34. A patient has two burns on his chest, one of which epithelialized in 1 week, the other in 3 weeks. The second wound now has a hypertrophic scar. Why?

Partial-thickness burns or abrasions that remain open for more than 2 weeks have a high incidence of hypertrophic scarring. Scarring is believed to be secondary to prolonged inflammation and can be minimized by rapidly closing a wound primarily, skin grafting, or other techniques.

35. What treatment options are available for hypertrophic scars?

Pressure garments, topical silicone sheeting, adjunctive use of insoluble steroids, and reexcision may improve hypertrophic scars. In general, simple reexcision and closure is a realistic solution if the cause of the scar was poor wound closure, inadequate support from wound tension, prolonged inflammation from infection, foreign bodies (excess suture), or delayed epithelialization. One should pay particular attention to using permanent sutures to splint the dermis, achieve early wound occlusion, and apply silicone gel sheeting.

36. What treatment options are available for keloid scars?

Proven treatment options include intralesional injection of steroids, radiation therapy, or combination therapy with surgical resection. More recently, interferon has shown some benefits in reducing collagen production and keloid thickness.

37. What effect does aging have on wound healing?

Aged patients have slower wound healing, less scarring, less contraction, decreased tensile strength, decreased epithelialization, delayed cell migration, and decreased collagen synthesis. Aging can be an advantage in performing cosmetic surgery because scarring can be minimized. However, it also can be a disadvantage because wound strength is lower, and a wound may easily be separated if placed under tension.

38. You perform a split-thickness skin graft (12/1000ths of an inch) for burns in a young patient and in an elderly patient, using the same technique and equipment. Several weeks later the young patient is doing well, but the elderly patient has blisters forming on the graft. What may be the cause?

Basal epidermal cells are attached to the underlying dermis by hemidesmosomes. Cells of aged individuals have been shown to be ineffective at forming new hemidesmosomes. Without an adequate dermal base, coverage of the wound by epidermis is unstable and characterized by chronic and recurrent breakdown. Therefore the skin of elderly patients is less tolerant to shearing forces. When shearing occurs, blisters are likely to form.

39. How does the fetal wound differ from the adult wound?

The main difference is that fetal wounds heal with little to no scar formation. Fetal wounds are bathed in amniotic fluid, heal with less inflammation, have increased levels of type III collagen, lack TGF-β, and have a relatively high content of hyaluronic acid.

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