Wound Healing: Part I. Basic Science

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Learning Objectives: After studying this article, the participant should be able to: 1. Describe the basic physiologic events in normal wound healing. 2. Understand the differences in healing among skin, bone, cartilage, and tendon. 3. Identify factors that may compromise or delay wound healing. 4. Describe methods for optimal closure of a wound.

Summary: Understanding the physiology and pathophysiology of normal wound healing and potential impediments to its end will allow the plastic surgeon to maximize postoperative outcomes and, in some instances, avoid unnecessary surgical interventions. Continuous advancements in our understanding of this process require frequent reviews of available data to permit reliable, evidence-based recommendations for clinical application. This is the first of a two-part article summarizing the science and clinical recommendations necessary for successful wound healing. (*Plast. Reconstr. Surg.* 138: 9S, 2016.)

Success in plastic surgery is founded on comprehensive understanding of one fundamental topic: wound healing. Whether the goal is reconstruction of a sternal defect, replantation of a detached finger, or aesthetic improvement of hypoplastic breasts, the surgeon's outcome ultimately depends on uncomplicated procession through normal wound healing. In the first of two articles on clinical wound healing, this overview offers the surgeon a practical guide based on the fundamentals of current scientific knowledge.

In order to prevent and treat pathologic wounds, it is first necessary to understand the basics of normal wound healing. An extensive quantity of literature has been published on the subject, attesting to its importance in treating surgical patients, developing wound care products or treatments, and evaluating current practices. Historically, wound healing has been arbitrarily divided into three phases, with some authors adding hemostasis as the inciting phase. Although wound healing occurs on a time continuum, division of the process into phases allows for ease of description and evaluation. Each phase is critical to the success of wound closure, and deviations from the norm may be associated with delayed or abnormal wound healing.

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BASIC WOUND HEALING

Hemostasis

Initial injury leads to disruption of the vascular endothelium and exposure of the basal lamina, which result in extravasation of blood constituents and concurrent platelet activation. While typically associated with clotting, aggregation and activation of these products also result in the subsequent release of growth factors involved in the deposition of extracellular matrix (transforming growth factor β), chemotaxis (platelet-derived growth factor), epithelialization (fibroblast growth factor and epidermal growth factor), and angiogenesis (vascular endothelial growth factor).[1]

Inflammation

Platelet activation is followed by an influx of inflammatory cells within the first 1 to 2 days, led by polymorphonuclear leukocytes. Neutrophils, as well as monocytes, fibroblasts, and endothelial cells, deposit on a fibrin scaffold formed by platelet activation.[2] Although they are the first to arrive in the wound, neutrophils are not foremost in the healing process. In a 1972 study, the absence of neutrophils was not shown to affect wound healing in uninfected wounds.[3] More recent studies support these findings and furthermore indicate that chemokines released by neutrophils are not required for healing, or may be supplied by other cells.[4] In fact, neutrophil activation may be

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responsible for release of free oxygen radicals and other cytokines that persist in chronic wounds.[5]

The presence of neutrophils is followed closely by that of monocytes, which are quickly activated into tissue macrophages. These cells are responsible for further tissue débridement and secrete additional cytokines and growth factors that promote fibroblast proliferation, angiogenesis, and keratinocyte migration (Table 1). Their presence is considered vital for wound healing, based largely on a study demonstrating decreased clearance of fibrin, neutrophils, erythrocytes, and other "debris" in wounds treated with antimacrophage serum.[6] They may also play a role in the apoptosis of neutrophils, thereby clearing cells that may otherwise result in a prolonged inflammatory stage.[7]

Proliferation

Proliferation is a broad term for a group of key steps that occur during this phase. Although they begin at various time periods in wound healing, collectively, epithelialization, angiogenesis, granulation tissue formation, and collagen deposition characterize proliferation.

Epithelialization is initiated by keratinocytes present on the wound edge as well as from dermal appendages, such as hair follicles, sweat, and sebaceous glands. This begins with cell detachment and mitotic division and is stimulated by epidermal growth factor, fibroblast growth factor, transforming growth factor β, and multiple cytokines. Fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor initiate and promote angiogenesis, which is of crucial importance for a healing wound.

Angiogenesis involves the formation of thin-walled endothelium from pre-existing vessels, in contrast to vasculogenesis, which indicates de novo vessel formation.

A healing wound is marked by increased metabolic requirements and is highly responsive to changes in oxygen supply.[8] Fibroblasts first appear in the wound after 24 hours[9] and require adequate oxygen supply for collagen production. In fact, without oxygen to assist in the hydroxylation of proline and lysine residues, chemical bonds will not form appropriately to create mature collagen. Fibroblasts are also responsible for elastin production and organization of the extracellular matrix.[10] These are all critical elements of granulation tissue and will serve as the basis for the final stage, maturation and remodeling.

Maturation and Remodeling

Appropriate wound maturation and remodeling result in a quickly healed and minimally visible scar, whereas prolongation of or deviations from this phase can cause hypertrophic or keloid scars or chronic, nonhealing wounds. Wound maturation requires the reorganization of newly deposited collagen into an organized, structurally sound lattice based on glycosaminoglycans and proteoglycans.

Initially, fibroblasts multiply and increase collagen production per cell.[11] This initial collagen is thinner than uninjured, mature collagen and lies parallel to the skin.[12] Type III collagen initially

Table 1. Summary of Inflammatory Cytokines*

Cytokine	Cells of Origin	Role in Inflammatory Response	Clinical Application
EGF	Platelets, macrophages, fibroblasts	Angiogenesis, re-epithelialization	Decreased in chronic wounds
FGF	Macrophages, mast cells, T lymphocytes	Fibroblast recruitment	Decreased in chronic wounds
IFNα	Monocytes, macrophages	Decreases collagen production	Used to treat hypertrophic/keloid scars
PDGF	Platelets, macrophages, fibroblasts	Fibroblast recruitment, myofibroblast stimulation	Recombinant form used to treat diabetic ulcers
TNFα	Macrophages, T lymphocytes, keratinocytes	Leukocyte chemoattraction	Elevated levels linked to deficient healing
TGFβ	Platelets, fibroblasts, macrophages	Re-epithelialization, wound fibroplasia	Elevated in hypertrophic and keloid scars
IL-1	Keratinocytes, neutrophils, macrophages	Leukocyte chemoattraction, wound fibroplasia	Increased in chronic wounds
IL-8	Macrophages, endothelial cells	Re-epithelialization, angiogenesis	Increased levels in delayed-healing wounds
IL-10	Monocytes, lymphocytes	Downregulation of other cytokines, limits fibroblast proliferation	Necessary for scarless fetal wound healing

EGF, epidermal growth factor; FGF, fibroblast growth factor; IFNα, interferon alpha; PDGF, platelet-derived growth factor; TNFα, tumor necrosis factor alpha; TGFβ, transforming growth factor beta; IL, interleukin.
*Derived from Henry G, Garner W. Inflammatory mediators in wound healing. *Surg Clin North Am.* 2003;83:483–507; and Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. *Wound Repair Regen.* 2008;16:585–601.

comprises 30 percent of the granulation tissue matrix,[13] compared with 10 to 20 percent in uninjured skin. Over time, the ratio of type III collagen decreases and that of type I collagen increases. An overall increase in collagen formation is seen for 4 to 5 weeks after wounding as wound strength increases, paralleling the increase in type I collagen. Breaking strength is only 3 percent at 1 week, but it increases to 20 percent after 3 weeks. Approximately 3 months after wounding, the wound reaches 80 percent of its uninjured counterpart but never reaches 100 percent.[2]

The strength of the wound is ultimately determined by the quality and quantity of collagen. Consequently, the fibroblast and its product have been labeled "the ubiquitous ally of the surgeon."[14] A specialized version of the fibroblast is also instrumental in the final size of the wound, as myofibroblasts are thought to lead to wound contraction. These cells, in contrast to normal fibroblasts, express alpha-smooth muscle actin, which enables the cells to contract. They are also thought to contribute to angiogenesis during wound healing by decreasing matrix metalloproteinase activity.[15]

BONE HEALING

While the basic tenets of wound healing apply to all tissues, certain distinctions of bone healing are critical for the surgeon using a free fibula for mandibular reconstruction, fixating a distal radius fracture, or grafting alveolar bone. Far from the inanimate structural prop that it is commonly treated as, the human skeleton is formed by a complex arrangement of living marrow surrounded by bone and periosteum.

After bone fracture, coagulation and inflammatory phases occur similar to those seen in disrupted skin. Fracture hematoma is replaced by a soft or fibrous callous as periosteal cells are stimulated to form osteoblasts. Intramembranous ossification occurs on the periphery of the fracture site.[16] Hard callus formation follows in 3 to 4 months, with endochondral ossification and the establishment of a bony bridge that stabilizes the fracture and prevents micromotion centrally. Hard callus formation is followed by bony remodeling, wherein woven bone is replaced by lamellar bone, similar to the process of exchanging the web of type III collagen for type I collagen in skin.

In order for this process to proceed unimpeded, fractured ends must be approximated and stabilized. Inadequate reduction, inadequate fixation, interposition of muscle or fascia, and local or systemic tissue alterations may result in nonunion.[17] When movement between the two fracture ends exceeds the strain allowable by the soft callus, hard callus will not form. Strain causes changes in the signals produced in the extracellular matrix and, depending on the degree of strain, will lead to fracture healing or fracture nonunion.[18] Inadequate reduction, with separation of bony fragments, does not allow appropriate strain to occur at the fracture site, and will also result in nonunion or malunion.

Clinically, inadequate bone healing can occasionally be resolved with the use of bone grafts. Grafts may be cancellous, cortical, or vascularized, and are selected depending on the defect. Advantages, disadvantages, and indications of these bone grafts are listed in Table 2.[19]

CARTILAGE HEALING

Unlike skin and bone, cartilage does not contain blood vessels. Oxygen and nutrients are delivered by diffusion, which limits cartilage's ability to grow and recover. Although cartilage often takes a backseat role in plastic surgery, it is of vital importance in rhinoplasty, ear reconstruction, otoplasty, and Mohs repairs. Small, full-thickness defects may be replaced by fibrocartilage, but cartilage defects usually result in the creation of a fibrous scar.[20] In animal studies, perichondrium has been reported to form new cartilage,[21,22] but this has not been successfully repeated in human studies. The prevalence of osteoarthritis in the U.S. population has made cartilage regeneration a lucrative target for investigation, but a clinical solution to the problem has not yet been produced. Recently, interest in adipose-derived stem cells has led researchers to explore their potential role in healing full-thickness cartilage defects,[23] and multiple studies involving stem cells[24–27] and growth factors have also been pursued.[28,29] If translated to the clinical spectrum, such advances may one day allow for facile repair of costochondral rib harvest sites or nasal deformities after trauma or rhinoplasty.

TENDON HEALING

Tendons were once considered comparable to cartilage, avascular and with limited capacity for healing. It is now known that tendons are made of tenoblasts and tenocytes in a network of extracellular matrix, and receive their blood supply from the musculotendinous junction and from the paratenon or synovial sheath.[30] Blood supply

Table 2. Bone Graft Properties*

	Revascularization	Incorporation	Common Harvest Sites	Typical Indications	Advantages	Disadvantages	Osteogenesis	Osteoinduction	Osteoconduction	Immediate Mechanical Strength
Cancellous grafts	Rapid, more complete (can occur within 2 days)	Creeping substitution (initiated by osteoblasts)	Iliac crest Femur Tibia Distal radius Rib	Nonunion Obliterating small defects or cavities	Rapid revascularization Conformability Low donor-site morbidity	Lack strength Limited supply Size limitations	Excellent	Excellent	Excellent	Poor
Cortical grafts	Slow, incomplete (can take up to 2 months)	Reverse creeping substitution (initiated by osteoclasts)	Iliac crest Fibula Calvaria Rib	Large bone gaps Need for immediate mechanical strength	Immediate mechanical strength	Slow revascularization Slow incorporation Loss of strength 6–12 months after surgery (stress fractures) Donorsite morbidity	Poor	Poor	Poor	Moderate
Vascularized grafts	Rapid (>90% of osteocytes remain viable in graft)	Process similar to normal bone healing and remodeling	Iliac crest Fibula Radius Scapula Medial femoral condyle	Large bone gaps (>6 cm) Composite defects	Immediate strength that persists Minimal graft necrosis Rapid incorporation Exhibit some normal healing and remodeling	Require expertise Long operative time Donor-site morbidity	Moderate	Moderate	Moderate	Excellent

*Reprinted from Buck D, Dumanian G. Bone biology and physiology: Part II. Clinical correlates. *Plast Reconstr Surg.* 2012;129:950e–956e.

is particularly relevant in the hand, as the dorsal aspect of the flexor tendons contains the principal blood supply, with a comparatively avascular volar zone.[31] Placement of core sutures in a dorsal location has consequently been demonstrated to result in significantly more tensile strength.[32] However, the limiting factor of successful tendon repair lies in the surgeon's ability to perform an atraumatic repair, in order to preserve the delicate blood supply.[33] Healing can occur via proliferation of epitenon and endotenon or extrinsically, by invasion of cells from the synovium. This is particularly relevant in the repair of zone II flexor tendon injuries, as extrinsic repair mechanisms may result in more scar and adhesion.

Both ex vivo and in vivo studies have shown superiority of the four-core suture in flexor tendon repair, with even greater strengths achieved in some six- and eight-strand core repairs.[34–36] Theoretically, placement of the knot within the repair site could affect intrinsic tendon healing, and a knot away from the repair site could create increased friction within the tendon sheath. However, conclusive studies have not shown knot location to affect final repair strength.[37,38] As with fracture healing, tendon repair is adversely affected by a gap separating the healing ends. Efforts to prevent gap formation in healing tendons have relied on strong core sutures and an epitendinous suture.[39,40] Epitendinous suture should not be relied on for final strength of the repair, as it only contributes 15 percent to the final strength, but it may decrease bulk at the site of repair and decrease early gap formation.[33]

As with bone, tendons show improved healing with some level of stress and motion after repair. Postoperative protocols have evolved from complete immobilization after flexor tendon repair to early active and passive range of motion. Practice patterns differ among surgeons, but studies have shown that early rehabilitation can accelerate the healing response and result in increases in final tendon strength.[41,42]

THE COMPLICATED WOUND

Ischemia and Hypoxia

Posttraumatic lacerations and abrasions of the face have been noted to have a marked ability to heal quickly and with limited sequelae. What differentiates injury to the cheek versus the distal leg is the abundant blood and, therefore, oxygen supply seen in the face. Based on the multitude of metabolic processes described above, it is no wonder that the healing wound is a hotbed of energetic

demand, requiring glucose and oxygen. Neutrophils and fibroblasts cease to function appropriately at low oxygen levels.[43,44] Clinically, reductions in oxygen tension correlate with unfavorable outcomes. Decreased subcutaneous oxygen tension results in higher rates of wound infection,[45] and collagen deposition is directly related to wound oxygen tension and tissue perfusion.[46]

While tissue perfusion is vital to wound healing, normal hemoglobin levels are not.[47] Although low hemoglobin levels are often associated with other conditions that impair wound healing, they do not necessarily diminish oxygen supply. The key to provision of oxygen and nutrient supply is arterial partial pressure of oxygen, not oxygen content, which often can be maintained by modifications in vasodilation, cardiac output, and capillary permeability. Vasoconstriction is damaging to the healing wound and can result from pain, cold, fear, nicotine, α1 agonists, β antagonists, and hypovolemia.[48] It is the surgeon's responsibility, therefore, to combat the above offenders to prevent local hypoxia and ischemia.

Infection

Bacterial proliferation within a wound bed can result in alterations to each phase of wound healing. Hemostasis can be altered through bacterial effects on platelets and complement. Bacteria can cause platelet agglutination and may also result in thrombocytopenia.[49] Bacteria also cause prolonged periods of inflammation and tend to alter the function of leukocytes through release of virulence factors. They also affect the formation of granulation tissue, and while they may actually increase collagen formation at a low level, Laato et al. found delayed healing at levels above 10^3 bacteria per milliliter.[50] The exact inoculum required for quantitative diagnosis of infection is debated but is typically accepted as 10^5 colony-forming units per gram of tissue for most bacteria. The exception is β-hemolytic streptococci, whose simple presence in a wound may indicate infection.[51]

Smoking

Cigarette smoke contains more than 4000 constituents, of which nicotine, carbon monoxide, and hydrogen cyanide contribute principally to disturbances in the normal pathway of wound healing.[52] Nicotine acts as a vasoconstrictor, resulting in local ischemia. Sarin et al. found a mean reduction in blood-flow velocity of 42 percent in digital vessels after smoking just one cigarette.[53] In addition, nicotine increases platelet adhesiveness, which can lead to thrombus formation and further decreases in blood delivery. It also has an inhibitory effect on the proliferation of erythrocytes, fibroblasts, and macrophages. Carbon monoxide, with a binding affinity 200 times greater than that of oxygen, binds to hemoglobin to produce methemoglobin and reduces oxygen delivery to the wound. Hydrogen cyanide inhibits oxidative metabolism and oxygen transport.[54]

As early as 1978, Mosely et al. reported delayed wound healing from nicotine exposure in a rabbit ear model.[55] Clinically, these detrimental cellular events are associated with higher rates of surgical-site infections and postoperative pneumonia,[56] wound necrosis after mastectomies,[57,58] and delayed or nonunion of fractures,[59–61] to name a few. Manassa et al. found a 3.2-fold increase in wound healing problems in smokers after abdominoplasty.[62] Kroll found rates of transverse rectus abdominis musculocutaneous flap necrosis that were nearly five times higher in smokers.[63] In order to obtain better outcomes, it seems only logical to advocate abstinence from smoking among surgical patients. Although there is no uniform guideline for the timing of preoperative abstention, an interval of 4 weeks before and 4 weeks after cosmetic or reconstructive surgery has been recommended.[64] Nicotine replacement therapy is commonly prescribed to assist with nicotine addiction, but its effects on wound healing are not clear. In an examination of blister exudate, metalloproteinase levels were elevated in smokers, but nicotine patch therapy had no effect on fluid exudate. Four weeks of abstinence normalized levels to those of nonsmokers.[65] The same investigator found higher levels of type I collagen in abstinent smokers treated with transdermal nicotine patches, but no increase in collagen was seen in abstinent smokers treated with a placebo.[66]

Diabetes

Diabetes affects the entire body and consequently affects the healing of all wounds. Multiple mechanisms have been implicated in its pathogenesis. Hyperglycemia results in the modification of proteins and enzymes, resulting in their dysfunction.[67] This also occurs at the level of the basement membrane, altering permeability and delivery of nutrients to the wound bed. Diabetics are also predisposed to microvascular and macrovascular disease, which can result in impaired blood flow and insufficient oxygen delivery.[68] Decreased blood delivery, hyperglycemia, and immune system impairments also make diabetics

more prone to postoperative infections.[69,70] Tight preoperative and postoperative glucose control may improve survival and decrease wound complications in comparison with sliding-scale insulin protocols.[71] Although exact target levels have been debated,[72,73] previously acceptable glucose levels of greater than 200 mg/dL are almost uniformly associated with worse outcomes and should be avoided.[74]

Nutritional Deficiency

While standard prealbumin and albumin measurements provide a starting point for nutritional evaluation, a detailed history may identify specific factors that contribute to wound healing complications. Surgery and trauma are known to increase metabolic demand and may make borderline deficiencies more significant. Protein malnutrition is of particular importance in the healing wound. In the 1930s, Thompson et al. showed a relationship between protein malnutrition and wound dehiscence in dogs.[75] Deficiencies in the amino acids arginine and glutamine are associated with compromised wound healing. This is because synthesis of these amino acids is insufficient during the periods of increased protein turnover that occur during wound healing.[76] However, while supplementation of arginine has been shown to increase wound breaking strength,[77] glutamine supplementation is controversial and has not been definitely associated with improvements in wound healing.[78]

Although protein supplementation is typically targeted in plastic surgery and wound healing, carbohydrates are the major source of fuel in the body and, therefore, wound healing. It has been estimated that a wound with a surface area of 3 cm^2 and a depth of 1 mm requires 900 kcal to produce the requisite collagen.[79] When glucose is not adequately supplied, the liver increases gluconeogenesis using the breakdown products of protein. Most postoperative patients will eagerly resume a diet when allowed, but it is important to provide the nothing-by-mouth patient with an adequate glucose supply, even if it is only through maintenance fluids.

The vitamin most closely associated with wound healing is vitamin C. Its association with scurvy was eloquently demonstrated by Crandon et al.[80]; Crandon, while working as a surgery resident, followed a diet containing no milk, fruit, or vegetables for 6 months. A biopsy at that time noted a lack of "intracellular substance," which returned after supplementation with 1 g of ascorbic acid per day.[80] Vitamin C has since been found to be a cosubstrate for hydroxylase enzymes required for collagen formation. The recommended dietary allowance of vitamin C is 60 mg, but supplementation in nondeficient patients is not conclusively beneficial in wound healing.[81,82] Vitamin A, in contrast, has been useful in nondeficient humans and animals.[83] These same authors demonstrated the benefits of vitamin A in promoting epithelialization and collagen synthesis in patients on steroids. It does not reverse the effects of steroids on wound contraction or infection.[84] The recommended dose of vitamin A is 25,000 IU by mouth daily preoperatively and for 4 days postoperatively.

Of the micronutrients, the key players in wound healing are zinc and magnesium. Zinc is a cofactor for RNA and DNA polymerase, and its deficiency decreases wound strength and epithelialization. It is a common component of Unna boots used for venous stasis ulcers. There is no evidence, however, that supplementation in the nondeficient patient improves wound healing.[48] Magnesium also functions as a cofactor in enzymes required for protein and collagen synthesis, and is used in some topical wound healing applications. As with zinc, its use as a supplement in the general surgical population lacks proven benefit.

Drugs

As alluded to above, steroids have a broad-sweeping negative effect on wound healing. Steroids decrease inflammation, inhibit epithelialization, and decrease collagen production. The clinical response to these molecular effects is an increase in dehiscence of surgical incisions, increased risk of wound infections, and delayed healing. Chemotherapeutic drugs would be expected to have a similarly extensive effect on wound healing, as many target DNA or RNA production, protein synthesis, or cell division. However, administration of chemotherapeutics is not synonymous with wound complications. Recent review of National Surgical Quality Improvement Program data showed no increase in wound complications after breast surgery in patients receiving neoadjuvant chemotherapy.[85] While early experimental evidence suggested the potential for diminished wound healing with chemotherapy,[86] clinical reports have not substantiated a detrimental effect.

Radiation

Ionizing radiation may be combined with chemotherapy, or used independently, to treat breast, prostate, skin, rectal, brain, and some lung cancers. As a result, a large percentage of the surgical

population has received or will receive radiation. The most important effect of radiation is its damage to DNA, which occurs as excited subatomic particles create chain reactions leading to single- or double-strand breaks or crosslinking of the double helix. Radiation also creates free radicals that damage proteins and cell membranes.[87] DNA repair enzymes repair some of the damage, but treatment generally overwhelms the body's reparative capabilities and results in microvascular damage, fibrosis, and atrophy.

Radiation acutely produces stasis and occlusion of vasculature, endothelial edema, and thrombosis.[88] Healing is decreased due to impairment in fibroblast proliferation, migration, and contraction.[89,90] These abnormalities lead to ineffective wound repair and slower epithelialization, decreased tensile strength, and higher infection and dehiscence rates.[91] The most effective treatment is limiting the extent of radiation damage in the first place. This has been accomplished by limiting the radiation field or using brachytherapy to target the radiation dose to the tumor.[92] Healthy tissues may also be protected against the damaging cytological effects of radiation by cytoprotective agents such as amifostine,[93] epoetin-α, and pentoxifylline. Therapeutic effects of adipose- and bone marrow–derived stem cells on radiation have also shown promise in case reports,[94,95] but large, controlled trials for either source are lacking.

SUMMARY

Obtaining optimal and expedient wound closure first requires a basic understanding of the physiology of wound healing. Surgeons in all specialties will improve outcomes and limit complications by adhering to preoperative and postoperative management strategies that incorporate the physiologic principles of wound healing. Look for an update on additional treatment adjuncts and biotechnology in Part 2 of this CME.

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