Wound Healing Primer

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KEYWORDS

• Acute wound • Phases of healing • Healing mechanisms
• Guidelines for healing

Surgeons often care for patients with conditions of abnormal wound healing, which include conditions of excessive wound healing, such as fibrosis, adhesions, and contractures, as well as conditions of inadequate wound healing, such as chronic nonhealing ulcers, recurrent hernias, and wound dehiscences. Despite many recent advances in the field, which have highlighted the importance of adjunct therapies in maximizing the healing potential, such as optimization of nutrition, growth factor therapy, advanced wound dressing materials, and bioengineered skin substitutes, conditions of abnormal wound healing continue to cause significant cost, morbidity, and mortality. To understand how conditions of abnormal wound healing can be corrected, it is important to first understand the basic principles of wound healing.

PHASES OF WOUND HEALING

Wound healing consists of a complex but very orderly array of overlapping phases in which highly specialized cells interact with an extracellular matrix to lay down a new framework for tissue growth and repair.[1] There are 4 distinct but overlapping phases of wound healing, which include hemostasis, inflammation, proliferation, and remodeling (**Fig. 1**). These phases are influenced by the various cellular interactions and are regulated by the local release of chemical signals such as cytokines, chemokines, growth factors, and inhibitors.[2,3]

HEMOSTASIS PHASE

Immediately after tissue injury, hemostasis occurs to minimize hemorrhage. While the blood vessels constrict, platelets are activated by binding to the exposed collagen in the extracellular matrix. The platelets then release fibronectin, thrombospondin, sphingosine 1 phosphate, and von Willebrand factor, which promote further platelet

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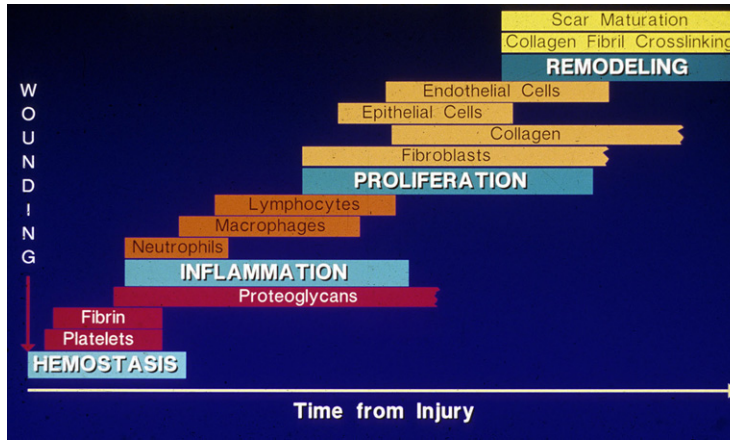

Fig. 1. Phases of normal wound healing. Cellular and molecular events during normal wound healing progress through 4 major integrated phases: hemostasis, inflammation, proliferation, and remodeling. (*From* Cohen IK, Diegelmann RF, Lindblad WJ, editors. Wound healing: biochemical and clinical aspects. Philadelphia: W.B. Saunders; 1993; with permission.)

activation and aggregation.[4] As these activation and other clotting factors are released, a fibrin matrix is deposited in the wound, which functions as a provisional matrix to stabilize the wound site. The aggregated platelets then become trapped in the fibrin matrix, thus forming a stable clot within the provisional matrix (**Fig. 2**).[5]

Several important mediators that are released by platelets are responsible for the initiation and progression of wounds through the subsequent phases of wound healing. These mediators include platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β). TGF-β and PDGF recruit additional cells, such as neutrophils and macrophages, to enter the wound. PDGF also recruits fibroblasts to the wound

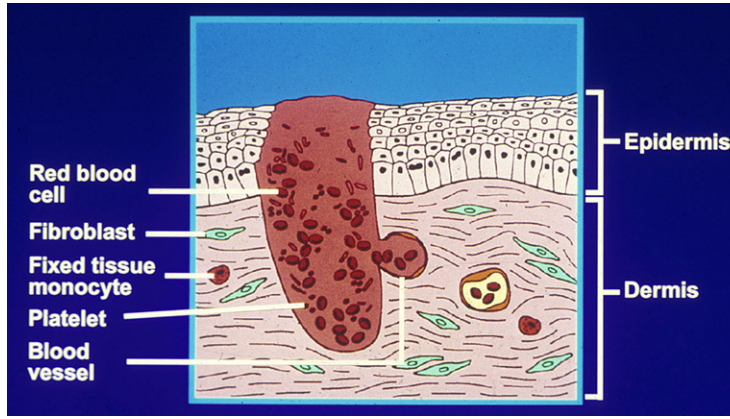

Fig. 2. Hemostasis phase. At the time of injury, the fibrin clot forms the provisional wound matrix and platelets release multiple growth factors that initiate the repair process. (*From* Greenfield, LJ, editor. Surgery: scientific principles and practice. Philadelphia: J.B. Lippincott, 1993; with permission.)

and activates the production of collagen and glycosaminoglycans by fibroblasts, which are important for the repair of the extracellular matrix.[2,3,6] Excessive levels of these growth factors have been indicated in conditions of abnormal wound healing; TGF-β is also present in many fibrotic conditions such as pulmonary fibrosis and cirrhosis.[7,8]

INFLAMMATORY PHASE

The next phase of wound healing is inflammation, which begins within the first 24 hours after an injury. The stage can last up to 2 weeks in patients whose wounds are healing appropriately but can last longer in those patients with chronic nonhealing wounds. From a clinical standpoint, this stage is characterized by rubor (redness), calor (heat), tumor (swelling), and dolor (pain), which results from the release of vasoactive amines and histamine-rich granules from the mast cells. These mast cell mediators cause surrounding vessels to become leaky and thus allow the efficient movement of neutrophils from the vasculature to the site of injury. Because the vessels become leaky, fluid also escapes into the area and thus causes the swelling (tumor) and pressure-causing pain (dolor).

In addition to mast cells, neutrophils and macrophages play key roles in the inflammatory phase (**Fig. 3**). Neutrophils serve as a first line of defense against infection by phagocytosing bacteria, damaged extracellular components, and foreign materials. As various chemical signals are released from the wound site, the endothelial cells in the nearby vessels are activated and begin to express specialized cell adhesion molecules (CAMs) called selectins. These CAMs function as molecular hooks to grab circulating neutrophils to bind to the endothelial cell surface by a process called pavementing. The adherent neutrophils begin to roll along the endothelial cell lining and then by a process called diapedesis, they squeeze through the cell junctions that have been made leaky by the mast cell mediators.[9,10]

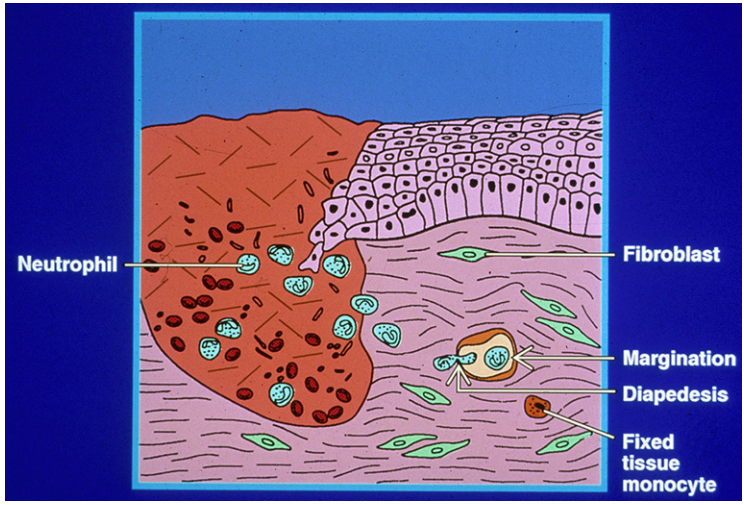

Fig. 3. Inflammatory phase. Within a day after injury, the inflammatory phase is initiated by neutrophils that attach to endothelial cells in the vessel walls surrounding the wound (margination), change shape and move through the cell junctions (diapedesis), and migrate to the wound site (chemotaxis). (*From* Greenfield, LJ, editor. Surgery: scientific principles and practice. Philadelphia: J.B. Lippincott, 1993; with permission.)

The neutrophils are attracted to the site of injury by a process called chemotaxis and are drawn there by soluble mediators, such as a breakdown product of a complement called C5a, a tripeptide f-Met-Leu-Phe (N-formyl-methionyl-leucyl-phenylalanine) that is a waste product produced by bacteria that may be present in the wound, and the potent chemokine interleukin (IL)-8.[11–13] To move through the extracellular matrix, the neutrophils release matrix-degrading enzymes, such as elastase and matrix metalloproteinase (MMP)-8, a collagenase. During a normal acute wound healing response, these enzymes are released in physiologic amounts and do not cause excessive tissue damage. In contrast, in many nonhealing chronic wounds, there is an overabundance of neutrophils, releasing massive amounts of these matrix-destroying enzymes that cause excessive damage to the extracellular matrix as well as the destruction of critical growth factors such as PDGF and TGF-β.[14–16] These ulcers are locked into a continuous inflammatory phase, resulting in extensive loss of tissue.[17]

On their arrival at the wound site, the neutrophils begin to aggressively phagocytize any foreign materials and kill bacteria by the powerful battery of enzymes and reactive oxygen species, which they can generate. The neutrophils actually initiate the first stages of the proliferative phase by releasing IL-1 and tumor necrosis factor (TNF)-α to begin the activation of fibroblasts and epithelial cells.

During the inflammatory phase, activated wound macrophages also play a key role in the regulation and progression of wound healing. Wound macrophages are derived from fixed tissue monocytes that originate from circulating monocytes (see **Fig. 3**). The wound macrophages are activated by chemokines, cytokines, growth factors, and soluble fragments of extracellular matrix components produced by proteolytic degradation of collagen and fibronectin.[18] The wound macrophages function to remove any residual bacteria, foreign bodies, and remaining necrotic tissue. The function of these macrophages is therefore similar to that of neutrophils, but macrophages better regulate proteolytic destruction of wound tissue by secreting protease inhibitors. In addition, macrophages ingest the bacteria-laden neutrophils and mediate progression of the wound from the inflammatory to the proliferative phase. Macrophages also secrete a multitude of growth factors and cytokines, such as PDGF, TGF-β, TNF-α, fibroblast growth factor (FGF), insulinlike growth factor 1, and IL-6, which then recruit fibroblasts and endothelial cells to the wound site for matrix deposition and neovascularization.

PROLIFERATIVE PHASE

The proliferative phase is characterized by fibroblast proliferation and collagen deposition to replace the provisional fibrin matrix and to provide a stable extracellular matrix at the wound site. The new matrix consists of collagen, proteoglycans, and fibronectins. In addition, angiogenesis occurs such that new blood vessels replace the previously damaged capillaries and provide nourishment for the matrix. Granulation tissue formation and the process of epithelization also occur.

Fibroblasts migrate into the wound in response to mediators released from the platelets and macrophages and move through the extracellular matrix by binding fibronectin, vitronectin, and fibrin via their RGD or arginine-glycine-aspartic acid amino acid sequence recognized by their integrin receptors (**Fig. 4**). The fibroblasts also secrete MMPs, which facilitate their movement through the matrix and help with the removal of damaged matrix components. Once the fibroblasts have entered the wound, they produce collagen, proteoglycans, and other components. Fibroblast activity is predominately regulated by PDGF and TGF-β. PDGF, secreted by platelets and macrophages, stimulates fibroblast proliferation, chemotaxis, and collagenase expression.

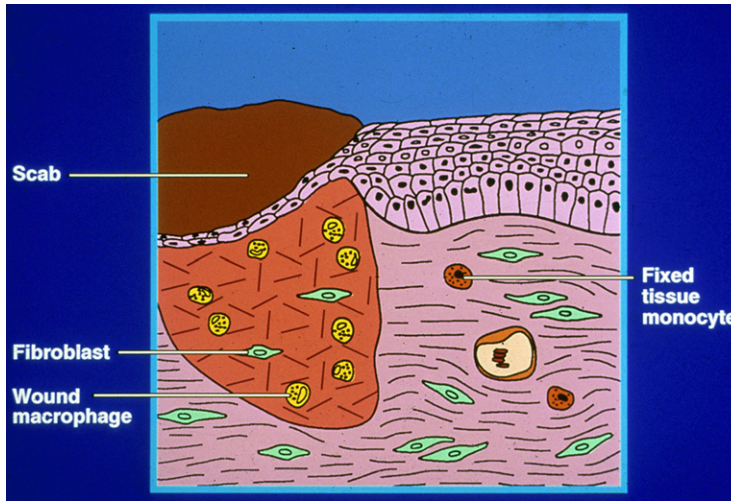

Fig. 4. Proliferation phase. Fixed tissue monocytes become activated, move into the site of injury, transform into activated wound macrophages that kill bacteria, release proteases that remove denatured extracellular matrix, and secrete growth factors that stimulate fibroblast, epidermal cells, and endothelial cells to proliferate and produce scar tissue. (*From* Greenfield, LJ, editor. Surgery: scientific principles and practice. Philadelphia: J.B. Lippincott, 1993; with permission.)

TGF-β has a central role in wound healing. There are 3 isoforms of TGF-β, which include TGF-β1, TGF-β2, and TGF-β3. TGF-β1 has been found to be present in excess amounts in conditions of fibrosis, such as pulmonary fibrosis and cirrhosis.[7,8] Although little is known about TGF-β2, TGF-β3 is associated with a reduction in fibrosis and scarring.[19] Despite their opposite effects on fibrosis, TGF-β2 and TGF-β3 bind the same TGF-β type 2 seronine/threonine kinase receptor, which then joins together with a TGF-β receptor (TBR) type 1 to activate the Smad cell signaling pathways.[20] Thus, activation of signaling cascades by the various TGF-β isoforms may account for the presence or lack of fibrosis within the wounds.

The most convincing studies that suggest a role for TGF-β in wound healing have been done in fetal animal models. Fetal mouse incisional wounds are known to heal without scarring and with a negligible amount of TGF-β present.[21,22] Lanning and colleagues[23] report that midgestational fetal wounds in the rabbit can be stimulated to contract in the presence of TGF-β1 and TGF-β3. In a study on the fetal mouse, rapid midgestational wound closure was associated with an increase in TGF-β1 and TBR-2 expressions compared with surrounding normal skin.[24]

Endothelial cells are activated by TNF-α and basic FGF (bFGF) to initiate angiogenesis such that new blood vessels are initiated to promote blood flow to support the high metabolic activity in the newly deposited tissue. Angiogenesis is regulated by a combination of local stimulatory factors, such as vascular endothelial cell growth factor (VEGF), and antiangiogenic factors, such as angiostatin, endostatin, thrombospondin, and pigment epithelium-derived growth factor. Local factors that stimulate angiogenesis include low oxygen tension, low pH, and high lactate levels.[25] Oxygen-sensing proteins regulate the transcription of angiogenic and antiangiogenic genes. Soluble mediators, such as bFGF, TGF-β, and VEGF, also stimulate endothelial cells to produce blood vessels. Tissue oxygen levels directly regulate angiogenesis

through hypoxia inducible factor (HIF), which binds oxygen.[26] When there is a decrease in oxygen levels surrounding capillary endothelial cells, HIF-1 levels increase inside the cells and HIF-1 binds to specific DNA sequences to stimulate VEGF transcription to promote angiogenesis.

As the wound continues to heal, the granulation tissue forms to provide the transitional replacement for normal dermis and ultimately evolves into a scar. Granulation tissue consists of a dense network of blood vessels and capillaries, elevated cellular density of fibroblasts and macrophages, and randomly organized collagen fibers. The metabolic rate is also higher for this tissue compared with normal dermis, which reflects the activity required for cellular migration, division, and protein synthesis and thus, the importance of adequate nutrition and oxygen to properly heal the wound.

REMODELING PHASE

The last phase of wound healing is the remodeling phase in which granulation tissue matures into a scar (**Fig. 5**). Small capillaries aggregate into larger blood vessels and there is an overall decrease in the water content of the wound. Similarly, cell density and overall metabolic activity of the wound decrease. Perhaps the most dramatic change occurs in the overall type, amount, and organization of collagen fibers, resulting in increased tensile strength of the wound. Initially, there is increased deposition of type III collagen, also referred to as reticular collagen, that is gradually replaced by type I collagen, the dominant fibrillar collagen in skin.[27] Collagen fibers are cross-linked by the enzyme lysyl oxidase, which is secreted by fibroblasts in the extracellular matrix. As the wound continues to remodel, changes in collagen organization increases the tensile strength to a maximum of about 80% of normal tissue.

Extracellular zinc-dependent endopeptidases called MMPs have recently emerged as an exciting area in wound healing, which may have promising therapeutic potential. MMPs control the degradation of extracellular matrix components to facilitate epithelial cell migration into the wound, angiogenesis, and overall tissue remodeling. MMPs

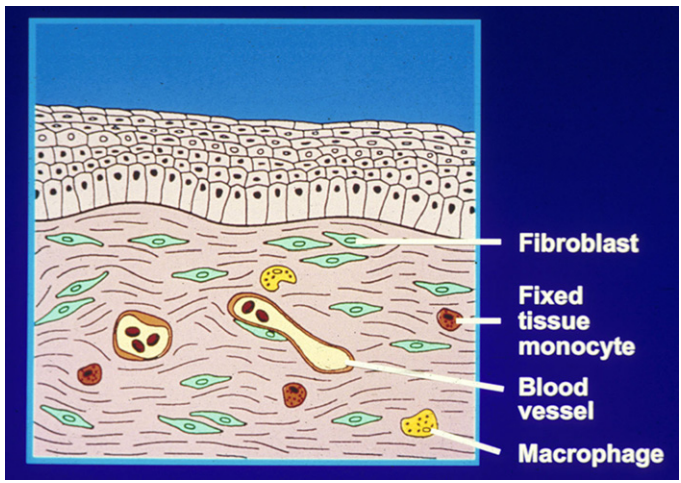

Fig. 5. Remodeling phase. The initial disorganized scar tissue is slowly replaced by a matrix that more closely resembles the organized extracellular matrix of normal skin. (*From* Greenfield, LJ, editor. Surgery: scientific principles and practice. Philadelphia: J.B. Lippincott, 1993; with permission.)

are secreted by epidermal cells and modulate tissue inhibitors of metalloproteinases (TIMPs) as well as degrade other growth factors.[28–31] Low levels of MMPs are found in normal tissue but increased levels of MMP-1 and MMP-2 are present in keloids, a condition of excess collagen deposition after cutaneous injury.[32] Similarly, a disruption in the balance between MMPs and their inhibitors has been reported in diabetic and venous stasis ulcers.[33,34] In addition, MMPs can be found in increased levels in chronic wounds.[35–38] Yager and colleagues[39] report that there are more than 10-fold higher levels of MMP-2 and 25-fold higher levels of MMP-9 in fluid from pressure ulcers compared with surgical wounds.

MMP expression is regulated by TGF-β. In normal fibroblasts and keratinocytes, abrogation of TGF-β1 is associated with decreased levels of MMPs and increased angiogenesis.[40–42] Tissue samples from keloids have demonstrated increased levels of MMP-2 and MMP-9 compared with healthy skin. Abrogation of TGF-β1 in keloid-derived fibroblasts results in a downregulation of MMP-9, further demonstrating the important relationship between TGF-β and MMPs.[43]

Treatment strategies targeted at the control of excess MMPs in chronic wounds have included the use of protease inhibitors to decrease MMP levels in the wounds and surrounding tissue. Oral and topical doxycycline, a potent MMP inhibitor, has been shown to decrease inflammation and matrix destruction.[44] Further studies are necessary to determine the clinical efficacy of doxycycline and other MMP inhibitors on chronic wounds.[45] TGF-β also minimizes matrix degradation by downregulating protease secretion and stimulating synthesis of TIMP.

As the extracellular matrix continues to remodel, collagen synthesis and degradation are ongoing as the matrix strives to achieve the original highly organized structure that was present before the wound injury. The scar tissue is always weaker than the normal surrounding matrix and can only achieve about 80% of the tensile strength that was present initially. If degradation maintains an equilibrium, then a fine line scar forms. If matrix synthesis is greater than degradation, then a hypertrophic scar may form. Conversely, if matrix degradation is greater than synthesis or if synthesis is inhibited by pharmacologic agents, such as steroids or cancer chemotherapeutic agents, or perhaps by malnutrition, the scar becomes too weak and wound dehiscence can occur.

MECHANISMS OF WOUND HEALING

Dermal wounds heal by 3 main mechanisms: connective tissue deposition, contraction, and epithelialization. Depending on the type of wound, these 3 distinct processes come into play to varying degrees. For example, an acute linear wound, such as a surgical incision that is closed by the surgeon using sutures, staples, tapes, or perhaps dermal glue, heals by what is termed primary intention. The major mechanism needed to heal wounds by primary intention is the process of connective tissue deposition. No contraction is needed because the surgeon has closed the incision by mechanical means. There is only minimal epithelization, which occurs along the wound line on the surface.

Open wounds, in which there is a loss of tissue, such as seen when a fingertip is injured, heal by a process termed secondary intention. These open wounds heal mainly by tissue contraction in which a centripetal force is generated by an interaction between fibroblasts and the matrix to advance the edges toward the center of the wound. There maybe some matrix deposition, and what is not achieved by those 2 processes is then covered by epithelization. Some chronic wounds, such as pressure

ulcers, also heal by secondary intention once the chronic inflammation is controlled and granulation tissue is allowed to form.

If an open wound is suspected to be contaminated with foreign debris or bacteria, then the wound must be kept open and treated with gentle irrigation until the foreign materials and infectious agents are removed. As a general guide, the total bacterial burden should be lower than 10^5 organisms/g of tissue, as determined by biopsy and culturing.[46] Surface swabs are generally thought to be inaccurate. The wound should be gently irrigated with saline or lactated Ringer, and pressures greater than 15 psi should be avoided because they can force materials deeper into the wound bed and also damage newly forming granulation tissue.[47] Once these goals are achieved and if the wound can be closed, then the wound heals by a mechanism termed delayed primary intention.

Epithelialization is the process whereby epithelial cells surrounding the wound margin or in residual skin appendages, such as rete pegs, hair follicles, and sebaceous glands, migrate into the wound because of the loss of contact inhibition of cuboidal basal keratinocytes.[48] This type of healing is termed partial thickness healing and is observed in minor abrasions and skin graft donor sites when an approximately 0.015 in thick piece of skin is removed for coverage elsewhere on the patient. After an extensive multistep process, these basal epithelial cells proliferate near the wound margin, producing a monolayer that moves over the wound surface.

DEFINITION OF WOUNDS

For many years, lack of uniform definitions in the generalized description of wounds served as an impediment in setting forth guidelines for the treatment of wounds. In 1994, the Wound Healing Society sought to standardize the definitions of wounds and the evaluation of wound healing. A wound is defined as a disruption in the normal anatomic structure and function. Wounds can be classified as acute or chronic based on whether or not they progress through an orderly and timely healing process so as to restore anatomic continuity and function. Wounds are further differentiated based according to whether they are ideally healed, minimally healed, or acceptably healed based on various degrees of restoration of normal anatomy, function, structure, and appearance.[49] The problems associated with diabetic venous stasis and other complex and difficult wounds are addressed elsewhere in this issue.

GUIDELINES FOR THE HEALING OF ACUTE WOUNDS

The Wound Healing Society identified 11 categories of impediment to wound healing to formulate guidelines to promote the healing of acute wounds.[50] These include local impediments such as wound perfusion, tissue viability, hematoma and/or seroma, infection, and mechanical factors as well as systemic impediments that include immunologic factors, oncologic factors, miscellaneous systemic conditions, thermal injuries, external agents, and excessive scarring. The following summarizes the main clinical recommendations of the published guidelines.

Adequate blood supply must exist to provide oxygenation and nourishment to healing wounds, which can be maximized for elective surgical wounds by ruling out clinically significant arterial disease by the presence of palpable pulses or ankle-brachial indexes greater than 0.9, calculated as the ratio of the resting systolic pressure in the arteries of the ankle to that of the brachial artery. The lack of sufficient blood supply may lead to tissue ischemia and an increased risk of infection. Similarly, hypotension in the setting of acute wounds should be minimized. Patients should be advised to avoid smoking, blood glucose levels should be controlled, and hypothermia should

be avoided, so to further maximize blood flow to the wounds.[51] The use of supplemental hyperbaric oxygen has long been thought to augment wound healing by increasing tissue oxygen levels; however, it has varied usage in the clinical setting. The Wound Healing Society guidelines suggest that more clinical data are necessary to support its use in acute wounds; however, a recent study demonstrated improved wound tissue oxygen tension in obese patients with supplemental oxygen administration.[52]

Wounds must be debrided of devitalized and infected tissue by one of the following methods, including preferably sharp surgical debridement and also enzymatic, mechanical, biologic or autolytic therapies. The formation of fluid collections, including hematomas, should be minimized by meticulous control of intraoperative hemostasis and correction of preoperative coagulopathies. Heparin prophylaxis against venous thromboembolism is indicated but may increase bleeding complications. There is no evidence according to the Wound Healing Society guidelines that antiplatelet agents increase the risk of hematomas. Similarly, the formation of seromas in patients with large skin flaps (mastectomy or component separation) should be minimized by closure of dead space and placement of surgical drains. The accumulation of fluid and blood may lead to local ischemia, necrosis, and an infected wound. Thus, postoperative fluid collections should be drained either surgically or percutaneously when possible.

Wounds should not be primarily closed if there is more than 10^5 bacteria/g of tissue or any amount of β-hemolytic streptococci because of an increased risk of wound infection.[46] A single dose of preoperative antibiotics is an indication in clean-contaminated or contaminated cases. Preoperative antibiotics are only recommended in clean cases if prosthetic materials, such as mesh, are implanted. Prophylactic antibiotics are not indicated in superficial nonbite injuries but should be used in bite injuries from animals and humans because they result in wound contamination. The risk of surgical site infections can further be decreased with normothermia and avoidance of hypoxia. Preoperative shaving of hair or scrubbing of the skin is not necessary to decrease the risk of infection because the bacterial load of normal skin flora is in the range of 10^3 organisms/g of tissue.

Wounds heal faster when closed primarily than those left to heal by secondary intention. Wounds should, however, be closed in a tension-free manner. Laparotomy incisions should be closed in a continuous manner using a suture length to wound length ratio of 4:1. The suture material used should be present until adequate tensile strength is obtained. The specific type of suture material used is irrelevant; however, permanent sutures are associated with an increased risk of fistulization. In patients with open abdomens, distractive forces that minimize subsequent fascial closure may be minimized through the use of negative pressure therapy. Retention sutures, long thought to be useful in preventing fascial dehiscence, do not prevent breakdown of the abdominal wall incisions.

Systemic immune defenses in patients with immune deficiencies should be maximized with the use of prophylaxis antibiotics, especially in patients with conditions such as AIDS. When possible, patients on immunosuppressants or steroid drugs should be weaned to the lowest possible dose preoperatively. Blood transfusions should be used with caution because they may result in transient immunosuppression.[53] Granulocyte-macrophage colony-stimulating growth factor may be used to correct leukopenia preoperatively so as to further maximize wound healing, but definitive studies have not been done to date.[54] In patients with cancer, operation performed through nonradiated tissue planes is associated with improved outcomes in wound healing. In addition, good nutrition is essential for optimal wound healing

and can be augmented using preferably enteral means. Good nutrition is especially important in elderly patients and in those with cancer. Nutrition has traditionally been assessed by the measurement of prealbumin; however, this marker has proved to be unreliable in conditions of inflammation, acute renal failure, and corticosteroid use,[55] There are also insufficient data to support exogenous use of vitamins unless there is clear documentation of specific nutrient deficiencies such as those of vitamin C.

Burn injuries can be characterized as complex wounds consisting of shallow-partial thickness wounds, deep wounds, donor-site wounds resulting from skin graft harvest, or interstitial wounds from skin grafts. Each type of wound requires a different type of treatment. Partial-thickness wounds typically epithelialize within 21 days, whereas deeper wounds may require debridement of necrotic tissue with subsequent skin grafting for tissue coverage. Early debridement of deep burns has been advocated to minimize infection risk from necrotic tissue and promote normal healing, which has been associated with improved survivals. Permanent skin substitutes or temporary biologic or biosynthetic dressings may be used as an alternative to skin grafting should the excited burn total body surface area be too large to allow for donor grating. Deep wounds that cannot undergo early debridement may benefit from topical antibacterial agents; however, these agents have not been shown to be beneficial on shallow wounds, donor sites, or meshed skin grafts. There is no role for systemically administered antibiotics in the absence of systemic infection. The role of various vitamins and cofactors to augment wound healing is controversial. Zinc therapy may improve wound healing in zinc-deficient patients, yet routine use of zinc is not indicated. There are insufficient data to support the definitive use of vitamin C, vitamin E, and arginine. Pressure garments or compression dressings may be used to decrease fibrosis and scarring in burn injuries requiring more than 21 days to heal. Proliferative scars may benefit from silicone sheeting to decrease fibroblast activity and downregulate TGF-β. Direct injection of corticosteroids, including triamcinolone acetonide (Kenalog), may also improve proliferative scars. Postoperative radiation for benign conditions must be used with extreme caution; however, laser therapy may be useful.

Improved healing has not been seen in children or elderly with scald burns as well as in those with either inhalation injury or burns to the face and hands.

NORMAL AND PATHOLOGIC RESPONSES TO WOUND HEALING

Acute wounds progress through the phases in an orderly fashion for normal healing to occur. Chronic wounds begin the healing process in a similar fashion; however, they have prolonged inflammatory phase in which there is significant destruction of the matrix elements caused by the release of proteolytic enzymes from the neutrophils.[14–17] Once the excessive inflammation is controlled by aggressive wound care, then the proliferative and remodeling phases begin; however, the resulting scar is often excessive and fibrotic.[56] These chronic nonhealing ulcers are examples of severely deficient healing and are addressed in detail elsewhere in this issue. Despite extensive research into the mechanisms underlying wound healing, patients continue to be plagued by such pathologic conditions of abnormal wound healing in other tissues and organs, including recurrent and incisional hernias, anastomotic leaks, and wound dehiscence.

In conditions of fibrosis, the equilibrium between scar deposition and remodeling is such that an excessive amount of collagen deposition and organization occurs. This condition leads to a loss of both structure and function. Fibrosis, strictures, adhesions,

keloids, hypertrophic scars, and contractures are examples of excessive pathologic healing.

Clinical differences between chronic and acute healing wounds are thought to be, in part, explained by alterations in the local biochemical environment. Acute wounds are associated with a greater mitogenic activity than chronic wounds.[57–59] Chronic wounds are associated with a higher level of proinflammatory cytokines than acute wounds. As chronic wounds begin to heal, they progress to a less proinflammatory state. Chronic wounds have elevated levels of MMPs compared with acute wounds.[16,39,56,60] Elevated protease activities in some chronic wounds may directly contribute to poor healing by degrading proteins necessary for normal wound healing, such as extracellular matrix proteins, growth factors, and protease inhibitors. Steed and colleagues[61] reported that extensive debridement of diabetic ulcers resulted in improved healing in patients treated with placebo or with recombinant human PDGF. Frequent debridement may therefore allow a chronic wound to heal in a similar fashion to an acute wound. In addition to the local wound environment, there are data to suggest that cells of chronic wounds may have an altered capacity by which to respond to various cytokines and growth factors and are in a senescent state.[62]

SUMMARY

The healing of surgical, acute, and chronic wounds requires the complex interaction of a multitude of cells, growth factors, and other proteins to allow the return of structure and function. Wound healing research only continues to evolve. With the creation of the Wound Healing Society guidelines as well as the significant contributions from researchers studying wound healing, the ability to modulate nonhealing wounds and facilitate wound closure continues to improve (http://www.woundheal.org).

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