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Soft Tissue Wounds and Principles of Healing

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Basic skin anatomy

Human skin is the largest organ of the body. It provides protection; thermoregulation; and sensory, metabolic, and immune functions and is a dynamic barrier for the underlying organism. Disruption of the skin by wounding can lead to fluid loss, infection, scarring, hypothermia, or compromised immunity [1]. A basic understanding of skin structure will help us understand the extent of injury and will help guide treatment and repair of wounds.

The skin is composed of two major layers: the outermost layer, or epidermis, and the dermis, which are separated by the basement membrane but are mutually dependent upon each other for skin integrity. The subcutaneous tissue that underlies the dermis and consists of adipose cells, fibroblasts, and macrophages and supplies the trunks for blood and nerve supply is termed the hypodermis. Skin appendages arise in the dermis and hypodermis and are derived from embryonic tissue that differentiates into eccrine and apocrine glands, hair follicles, and nails.

Epidermis

The epidermis is derived from ectoderm. It is a stratified epithelial layer that can range in thickness, depending upon the sex and the anatomic location, from approximately 0.05mm to 0.75mm, depending upon the

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source you read. This layer is avascular, and the classically identified layers are the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale.

The outermost layer or stratum corneum is composed of anucleate, keratinized, dead cells surrounded by a cornified envelope called keratinocytes or squames. This layer is several layers thick and is continuously shed, with replacement cells from the underlying layer migrating outward at about the same rate as the dead cells are sloughed form the outermost layer. This layer is resistant to pH changes, temperature, and dehydration. The stratum lucidum underlies the stratum corneum and is an area of remodeling. This is a relatively thin layer and may be absent or patchy upon electron microscopy of thin skin. The stratum granulosum or granular layer underlies the lucidum and is characterized by flat cells with active metabolism. The cells are filled with keratin, and, as they move through this layer, they lose their nuclei and organelles. The stratum spinosum contains cells with spine-like structures that are desmosomes with connections to the surrounding cells. This layer is mitotically active and gives rise to the granulosum as it moves outward. The stratum basale or basal layer is a single cell thick. It is here that keratinocytes divide and begin differentiation. Cells of this layer are pushed outward to give rise to the stratum spinosum. This layer has areas of ingress into the underlying dermis called epidermal ridges, which are intercalated with the dermal ridges. The two layers are separated by a thin basement membrane, which is a semipermeable membrane that regulates the transfer of proteins and other materials across the dermal–epidermal junction. Because the epidermis is avascular, it depends upon diffusion from the capillary beds of the dermis for its blood supply.

Keratinocytes, which are responsible for the production of keratin, are the most populous cell of the epidermis. Langerhans cells, dendritic cells derived from the bone marrow that are part of the reticuloendothelial system, possess an antigen-processing capability and are interspersed among the keratinocytes. Melanocytes arise from neural crest and produce the primary skin pigment melanin. The melanocytes transfer pigment to the surrounding keratinocytes via pinocytosis. Merkel cells for afferent nerve conduction and mechanoreception are found in the basal layer as well.

Dermis

This layer of skin is composed of dense collagenous connective tissue. It is further subdivided into a papillary layer that interdigitates with the epidermal ridges via dermal ridges and secondary dermal papillae and a denser layer termed the reticular layer. Blood supply from the reticular layer enters the papillary layer's dermal ridges to supply blood to the overlying epidermis. The reticular layer supports a vascular plexus that is supplied from the underlying hypodermis. Hair follicles, sebaceous and eccrine glands, and Pacinian corpuscles are present in this layer.

Dermal nerves and vasculature

The cutaneous nerve supply travels along the blood supply to the skin. The source is a single segment of the spinal cord and is the well known "dermatome." The terminal nerve branches along with several specialized sensory structures, including Merkel cells and Meissner corpuscles for light touch, Pacinian corpuscles for pressure detection, Raffini corpuscles for heat detection, thermoreceptors for the detection of heat and cold, and naked nerve endings for the sensation of pain are present in the dermis and basal layers of the epidermis.

Cutaneous vessels arise from underlying vessels derived from septocutaneous or fasciocutaneous perforator vessels or from terminal branches of the musculocutaneous vessels. The terminal branches form the extensive superficial vascular plexus and the deep vascular plexus, which is interconnected to the superficial plexus by vertical dermal vessels and forms a continuous vascular network within the skin. This vascular network is responsible for the thermoregulatory property of the skin. Vasoconstriction and vasodilatation of these vessels are under the control of the hypothalamus. Glomus cells are a specialized vascular structure that is basically an arteriovenous shunt connecting an arteriole and a venule and when open cause and increase in blood flow in the area.

Lymphatics also parallel the blood supply to the skin and are a functioning component of the reticuloendothelial system. Following the pattern of the blood vessels, they become increasingly larger in caliber as they move deeper into the dermis and subcutaneous tissue and ultimately drain into the venous circulation.

Subcutaneous tissue

Mature subcutaneous fat makes up the bulk of the subcutaneous tissue. The lobules that form the subcutaneous layer are separated by thin, fibrous septae through which the vessels and lymphatics course. The septae provide a structural framework that stabilizes the subcutis, compartmentalizing it and connecting the reticular layer of the dermis to the fascial planes that underlie the subcutaneous fat [2]. This layer varies in thickness in various anatomic positions and in individuals.

Epithelial appendages

After injury, reepithelialization is essential to reestablish the barrier function of the skin. This involves cellular migration from wound edge to wound edge and involves epithelial cells derived from the epithelial appendages, such as hair follicles and apocrine and eccrine glands.

Types of wounds

Wounds can be classified as acute or chronic. Acute wounds can be defined as any interruption in the continuity of any tissue of the body [1].

This is in contradistinction to a chronic wound, which can be defined as an interruption in the continuity of any tissue that requires a prolonged time to heal, does not heal, or reoccurs [1].

Acute wounds heal as anticipated and proceed through a normal, orderly, and timely reparative process that results in sustained restoration of anatomic and functional integrity. Chronic wounds do not heal as anticipated and fail to proceed through this process or proceed through the process but fail to establish a sustained anatomic and functional result [3]. Chronic wounds may get stuck in any of the phases of wound healing for greater than 6 weeks [4].

Acute wounds

Lacerations are usually caused by a simple shearing force (eg, from a knife or glass). This is a simple dividing of tissue. There is little kinetic energy imparted to the tissue, so the surrounding tissue injury is minimal, although glass injuries can cause significant damage to soft tissues [5]. Partial avulsion lacerations are complicated lacerations in which the dermis has undergone a significant separation from the superficial fascia, creating a ''flap of dermis.'' This wound can compromise the flap of tissue because its remaining blood supply is derived from the intact dermal portion at the base of the flap. In random flaps, clinical experience has resulted in the observation that the ratio of flap length to width is critical for complete flap survival [6]. This rule varies from anatomic site to anatomic site.

Tension injuries are a result of a blunt or semi-blunt object striking the skin at an angle. Often a triangular flap is created, and the blood supply is interrupted on two sides of the flap [7]. Crushing or compression injuries occur when a relatively blunt object strikes the skin at a right angle [7]. These lacerations often have ragged or irregular edges, and a significant amount of kinetic energy is transferred to the surrounding and underlying tissue. Shearing force is a mechanical force that is parallel rather than perpendicular to an area. This may cause a triangular-shaped flap or tunneling.

Puncture wounds

Puncture wounds account for 3% to 5% of all traumatic injuries presenting to pediatric emergency rooms [8]. Most are on the plantar aspect of the foot. Puncture wounds are commonly caused by nails but can also occur via envenomation; human and animal bites; iatrogenic causes; and foreign bodies such as wood, metal, glass, and plastic. One must be vigilant to suspect a retained foreign body if the mechanism of injury suggests it.

Bite wounds

Bite wounds are one of the most common types of trauma [9]. The majority of such wounds are caused by dogs, cats, and humans and often involve young children. The mechanism of injury can frequently cause

crushing, tearing, or avulsion of tissue and cause devitalized tissue with significant bacterial contamination.

Abrasions

Abrasions are skin wounds caused by a tangential force to the epidermis and dermis. The skin surface is forced against a resistant surface and essentially scraped away. Varying thicknesses of epidermis and or dermis can be lost, and deeper abrasions can occur. Abrasions can cover a significant amount of total body surface area and are frequently impregnated with grass, asphalt, and dirt.

Burns

A burn is damage to the skin and underlying structures caused by excessive heat or caustic chemicals. Burns are usually divided into three depths of tissue injury. Superficial or epidermal burns, typified by the common sunburn, are confined to the epidermis. Partial-thickness burns involve the epidermal layer and part of the dermal layer (formerly referred to as second-degree burns). This can further be divided into two depths of partial thickness burns: superficial partial thickness and deep partial thickness. Superficial partial thickness burns involve destruction of the epidermis and the upper one third of the dermis. Blisters form in this type of burn. Deep partial thickness burns destroy epidermis and most of the dermal layer. As a result, the wound is white and dry. Full-thickness burns are burns in which the epidermis, dermis, and epidermal appendages have been destroyed. This burn is waxy and white. Subdermal burns involve destruction of outer epidermis and dermis and extend to the tissue below, including fat, tendon, muscle, and bone.

Burn severity is determined by depth of burn, total body surface area burned in percent, location of burn, and patient age. The rule of nines is a commonly used tool to divide the surface of the body into segments of 9%. Age is a major factor in determining the prognosis of the burn, with infants and elderly individuals at higher risk for a mortal event. The depth of heat or caustic injury depends upon the quantity of heat exposure and depth of heat penetration. Location of the burn with respect to anatomic function and depth of overlying skin also plays a role in the severity of burn. Initial evaluation of a burn patient in the emergency department may underestimate the severity of the burn. The wound may involve deeper structures than can be estimated upon primary evaluation. Burns are dynamic and can evolve into deeper wounds over time depending upon the initial injury and subsequent environmental insults [10].

Chronic wounds

Chronic wounds arise from acute wounding if appropriate interventions are not initiated or if factors known to delay healing predominate. Chronic

wounds often occur in individuals who have underlying comorbidities, including advanced age, peripheral vascular disease, malnutrition, diabetes, chronic steroid use, or other chronic diseases that impair tissue healing. Chronic wounds do have differences at the cellular level that distinguish them. Chronic wounds do not have clot formation, which diminishes the growth factors present in platelets and "primes the wound for healing" [1].

Debridement can improve healing by exposing viable tissue [11]. Most chronic wounds are colonized with bacteria and thus require more macrophages and immune response to be mounted to clear away debris, contributing to prolonged healing time [1]. Increased epithelialization, which increases scar friability and the need for increased angiogenesis, can also prolong wound healing. Chronic wounds generally have extensive tissue loss and extensive tissue remodeling.

Pressure ulcers

A pressure ulcer is a disruption of the normal anatomic structure and function of skin that results from an external force associated with a bony prominence that does not heal in an orderly and timely fashion [12]. Pressure ulcers can be categorized according to the National Pressure Ulcer Advisory Panel definitions.

STAGE 1: An observable pressure-related alteration of intact skin, with indicators such as an adjacent or opposite area on the body, which may include changes in one or more of the following: skin temperature (warmth or coolness), tissue consistency (firm or boggy feel), or sensation (pain, itching). In lightly pigmented skin, the ulcer appears as a defined area of persistent redness, whereas in darker skin tones, the ulcer may appear with persistent red blue or purple hues.

STAGE 2: Partial-thickness skin loss involving the epidermis, dermis, or both.

STAGE 3: Full-thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to but not through the underlying fascia.

STAGE 4: Full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures.

Diabetic foot ulcers

Diabetic foot ulcers typically occur on the plantar aspect of the foot in areas prone to excessive pressure. They generally present as symmetric, round, puncture-appearing wound cavities with a clean wound bed and callous around the wound. Atherosclerotic occlusive disease is a factor in the development of malperforate ulcers; however, the combination of autonomic neuropathy, infection, and autonomic dysfunction that produces anhydrosis and hyperkeratosis also contributes to the development of this

wound. Diabetic patients typically manifest lesions in the distal popliteal and tibioperoneal arteries, with usual sparing of the dorsal foot.

Venous insufficiency ulcer

Venous insufficiency ulcers are typically partial-thickness wounds resulting from chronic venous insufficiency. They are usually located between the mid calf and malleolus. They have shaggy, irregular borders and often have heavy exudates [13]. There is a brownish pigmentation of the skin secondary to extravasated hemoglobin and loss of subcutaneous fat, leading to lipodermatosclerosis. Although there is unanimous agreement that venous ulcers are due to venous stasis and back pressure, there is less consensus as to the exact pathophysiology that leads to ulceration and impaired healing [14].

Ischemic wounds

Ischemic wounds are generally atrophic and can lead to necrosis of the affected part. The wounds are generally shallow, painful, have a pale base, and are usually caused by a decrement in blood supply to the affected body part. The wounds are commonly present on the most distal portions of the extremities, although more proximal locations are encountered. Other signs of peripheral ischemia, such as dryness of the skin, hair loss, scaling, and pallor, can be present [14]. Occlusive disease is often manifested in the superficial femoral system, often in the adductor hiatus or Hunter's canal.

This brief introduction of the anatomy and types of wounds will help in the evaluation of wounds seen in the emergency department. Knowledge of skin structure can help to define the depth of injury and informs the clinician of the extent of repair that must occur to restore tissue health [1].

Principles of wound healing

Patients presenting to the emergency department commonly have wounds. In a British study of presenting problems, a surprising statistic was reported. Twenty-five percent of the 11 million patients attending Accident and Emergency Departments in England and Wales present with wounds [15]. It behooves the emergency physician to have a thorough working knowledge of principles of wounding, initial wound management, and management of complications from wounds.

In addition, our world seems to be getting smaller, with rapid evacuation from global military conflicts. Due to protective body armor, soldiers may suffer injuries in areas of the body not covered by armor. Frequently these are soft tissue injuries. In combat casualties in Afghanistan during Operation Enduring Freedom, fragments were the most common mechanism of injury (49%), with the extremity as the most common location of injury (58%) [16]. There have been reported unique injury patterns (behind armor blunt trauma) to

the victim wearing body armor. These injuries have some of the features of blunt chest trauma and have characteristics of primary blast injury [17].

Physicians should be facile with the management of wounds of any type that present to our care, and it is to the history of this topic we now turn.

History of wound management

Humans have always experienced wounds of some type, whether accidental, from interpersonal trauma, burns from heat sources, or even self-inflicted wounds for attention seeking or for cultic reasons. Wounds readily lend themselves to observation and study. In different ancient societies, there are those who practiced healing arts. The Assyrian cuneiform scripts define laws for practicing wound healers who, like the Egyptians, were definitive in their teaching of the need to drain pus [18]. In some cases, healers felt that different materials were useful to be placed on wounds. Some of these included plant materials or animal feces. Due to this practice, many of their patients contracted tetanus. The first tetanus toxoid (inactivated toxin) was produced in 1924 and was used successfully to prevent tetanus in the armed services during World War II [19]. Before the tetanus vaccine was in use, many patients probably died from inoculation from materials that contained the *Clostridium tetani* endospores.

Hippocrates taught that cleanliness and, to some extent, aseptic technique was important. He realized that wounds could heal primarily but also practiced wound irrigation with antiseptics such as vinegar and wine in preparation for delayed primary or secondary closure [20].

Despite much being known about wounds and wound care, there is much to be learned concerning the intricate interplay and interactions that result in a healed wound. Much is also known about factors that lead to chronic wounds and their clinical manifestations (Box 1), but we still have a great

Box 1. Clinical features of nonhealing wounds

Absence of healthy granulation tissue
Presence of necrotic and unhealthy tissue in the wound bed
Excess exudates and slough
Lack of adequate blood supply
Failure of reepithelialization
Cyclical or persistent pain
Recurrent breakthrough of wound
Clinical or subclinical infection

Data from Grey JE, Harding KG. ABC of wound healing; wound assessment. BMJ 2006;332:285–8.

deal to learn about how to convert nonhealing, painful, and resource-taxing wounds into wounds that heal.

Wound healing and phases

Normally, wound healing lasts for up to 2 years, but nutritional and metabolic factors delay healing; hyperalimentation would likely be beneficial under these conditions. Other factors that influence wound healing are the oxygen tension in tissues, the hemodynamic status, and the effects of substances such as cortisone, vitamins A and C, and zinc [21]. Nutrition is a factor that globally affects wound healing. Vitamins and trace minerals can have harmful effects and are discussed in the appropriate section.

To study wounds and to be able to describe phases of healing, various phases have been promoted by different investigators [22,23]. The author prefers to use the phases as described by Jorgensen [24] because the differentiations are most inclusive. Wound healing encompasses coagulation, inflammation, angiogenesis, fibroplasia, contraction, epithelialization, and remodeling. These phases are discussed in detail in the sections that follow.

Hemostasis/coagulation

Excessive bleeding is deleterious to the patient's well-being; however, in the heat of battle in the emergency department and in the transfer process, wounds that seem innocuous, such as digit or scalp wounds, can have significant bleeding. It is beyond the scope of this article to cover techniques that effect hemostasis.

After the injury, the damaged blood and lymphatic vessels undergo vasoconstriction to slow or stop blood loss in the affected area. Norepinephrine secreted by blood vessels and serotonin secreted by platelets and mast cells are responsible for the vasoconstriction of the vessels [25].

As the blood components spill into the site of injury, the platelets come into contact with exposed collagen and other elements of the extracellular matrix. Different tissues that are exposed for contact with platelets activate the extrinsic versus the intrinsic pathway. Exposed tissue plays a dominant role in hemostasis. In the tissues that are exposed from wounds involving the brain, lung, placenta, heart, and uterus, a tissue complex between tissue factor-factor VIIa forms a complex, and hemostasis is achieved using the extrinsic pathway. Skeletal muscle and joint tissue hemostasis involves factor VIIIa and factor IXa complex [26].

Contact between these complexes with platelets causes the release of clotting factors and essential growth factors and cytokines, such as platelet-derived growth factor (PDGF) and transforming growth factor–β (TGF-β) [27]. These growth factors are important triggers not only for hemostasis, but as important messages for the later phases of healing.

It is important for platelets and the coagulation cascade to initiate wound healing. This first phase is much like the moment when the orchestra tunes to begin a performance. The insult has occurred, the platelets and clotting cascade join in and crescendo to form a clot, and then there is silence as the next phase of inflammation begins.

There are clear factors that we can pinpoint that adversely affect clotting and the coagulation cascade. Some patients have hereditary conditions (eg, hemophilia) that affect these clotting factors. The coagulation cascade has numerous components, and there is current scientific interest in controlling these factors in patients who have cerebrovascular, coronary, or atherosclerotic disease. In our current environment, many elderly patients are on aspirin. Platelets that have been exposed to certain medications are ineffective, whether poisoned by aspirin or other agents such as ticlopidine, dipyridamole, and clopidogrel [28].

For most of the wounds we deal with, the vessels have been cut, torn by traction, or abraded. In practice, these vessels heal in what we would understand as a ''normal'' process. However, electrical injury produces a unique pattern of injury. Vascular injury by electricity is a thermal process extending from the interior to the exterior [29]. This factor should affect the way electrically injured wounds heal.

In the normal patient, the orchestra has come to a crescendo in tune from the interplay with the platelets and the coagulation factors providing hemostasis/coagulation, and chemical signals have been sent to recruit the other factors in healing. Silence prevails for the moment as the conductor turns to the sheet music of wound healing whose first stanza is inflammation.

Inflammation

After hemostasis, the neutrophils enter the wound site and begin the critical task of phagocytosis to remove foreign materials, bacteria, and damaged tissue [27]. This point signals the initiation of the inflammatory phase. There are numerous inflammatory mediators and chemical signals, many of which are probably not delineated yet. Leukemia inhibitory factor, interleukin (IL)-6, IL-11, and possibly other members of this cytokine family are key mediators in various inflammatory processes, such as the acute-phase reaction, tissue damage, and infection [30]. IL-6 and cortisol seem to act synergistically to activate the acute-phase response. A systemic role for IL-1 and tumor necrosis factor is not evident, even if the possibility that these lymphokines may act locally has not been ruled out [31]. Other inflammatory mediators, such as kallikrein kininogen, are present in wounds and kinin receptors, such as kinin-B1 [32].

The inflammatory phase must be temporary. If there is an infection or other inflammatory process active, this retards wound healing. The risk of infection in traumatic wounds is reduced by adequate wound cleansing and debridement with removal of any nonviable tissue and foreign material

[33]. Wound cleansing should be done by solutions that are not tissue toxic or antigenic. The use of povidine-iodine should be discontinued because it is tissue toxic. Better alternatives include nonionic detergents or chlorinated tap water [34]. The goal is to physically remove any foreign material that could lead to increased inflammation and to decrease bacterial counts.

Some suture materials that have been in use for a significant period of time have been found to have excessive inflammatory properties. Catgut should no longer be used because it causes an excessive tissue reaction, which may predispose to infection [33]. Silk can cause an intense tissue reaction, with an increased risk of excessive scarring and of formation of a suture abscess; silk is therefore no longer recommended [33].

Angiogenesis

The next phase of healing involves the creation of vessels and repair of damaged vessels. Any military historian can tell you that the most critical factor in successful military campaigns is the ability to supply troops in the field. The same principle applies to wound healing. The tissues need tissue oxygen and nutrients and removal of carbon dioxide and waste products.

The adhesion of platelets to the denuded subendothelial matrix is the hallmark of the acute phase providing an adhesive substrate for monocytes, whereas chronic monocyte recruitment is regulated by the interaction with neointimal smooth muscle cells and recovering endothelial cells [35]. These monocytes are key players in the process of angiogenesis. In addition, vascular endothelial growth factor (VEGF) is important and is believed to be the most prevalent angiogenic factor throughout the skin repair process [36]. The lack of α_2-antiplasmin markedly causes an over-release of VEGF from the fibroblasts in cutaneous wound lesions, thereby inducing angiogenesis around the area and resulting in an accelerated wound closure [37].

Factors that adversely affect angiogenesis

The dictum ''if some is good, more is better'' does not apply to the critical process of angiogenesis. The exuberant infiltration with monocytes aggravates neointimal growth and can thereby promote restenosis [35].

Elderly patients heal slower than younger patients. This may be related to delayed angiogenesis. In the aged mice model, a decline in angiogenic growth factor production and a decline in endothelial responsiveness to specific factors may account for the delayed wound angiogenesis. These results indicate that age-related alterations in macrophage function might partially account for the overall delay in the wound repair process [38].

Protamine sulfate given in high doses can inhibit angiogenesis in the granulation tissue generated in an open wound. The abnormal vasoformation that may be initiated by protamine's anticoagulant properties could set the stage for impaired fibroblast synthetic activity [39]. It is to the fibroblasts, which are the agents of collagen construction, that we now turn.

Fibroplasia/fibroproliferation

As part of the inflammatory phase, the macrophages appear and continue to process of phagocytosis and release more PDGF and TGF-β. Once the wound site is cleaned out, fibroblasts migrate in to begin the proliferative phase and deposit new extracellular matrix. The new collagen matrix becomes cross-linked and organized during the final remodeling phase [27].

Nitric oxide in the inducible isoform is synthesized in the early phase of wound healing by inflammatory cells (mainly macrophages) and regulates collagen formation, cell proliferation, and wound contraction [40].

The results are consistent with the hypothesis that control of collagenase (matrix metalloproteinase-1) expression is important for reepithelialization during wound healing and indicate that collagenase regulation is critical to the kinetics of normal wound closure [41].

Factors that adversely affect fibroproliferation

Agents that are toxic to cells that provide the extracellular matrix should not be used in wound care because this can deleteriously affect wound healing. Shur-Clens, SAF-Clens, and saline were found to be the least toxic to fibroblasts (toxicity index 0); Dial Antibacterial Soap and Ivory Liqui-Gel were the most toxic (toxicity index 100,000) [42].

Experimental wounds in aged mice have age-related changes in scar quality and inflammatory cell profile that are similar to those seen in fetal wound healing. Despite an overall decrease in collagen I and III deposition in the wounds of old mice, the dermal organization was surprisingly similar to that of normal dermal basket-weave collagen architecture. By contrast, young animals developed abnormal, dense scars. The rate of healing in young animals seems to be increased at the expense of the scar quality, perhaps resulting from an altered inflammatory response [43].

The nutritional state of the patient has been felt to be important in wound healing. Patients who are malnourished have delayed healing. Proteins and cofactors are required in wound healing. Due to the link with scurvy, physicians have felt that vitamin C in high doses might be useful [44–47]. It is not clear how much vitamin C is helpful, and supplemental ascorbic acid in the seriously ill patient can result in renal failure [48].

Nutrition is linked with promoting wound healing. In a randomized, placebo-controlled, double-arm, crossover study, subjects responding to oral supplements had less redness in the wounds observed that may have been associated with less inflammation, and 70% of normal, healthy subjects studied had accelerated soft-tissue wound healing [49].

Some patients have excessive scar formation, and plastic surgeons or dermatologists want to intervene to decrease the risk of keloid formation. 5-Fluorouracil, a pyrimidine analog widely used in cancer chemotherapy and in glaucoma surgery, has recently shown some efficacy in the treatment of keloids, scars that overgrow the boundaries of original wounds [50].

Other treatments for keloids include silicone gel sheeting, elastic garments, steroids, radiation therapy (1200–2000 gy in five doses), and bleomycin [51].

Beta blockade with propranolol has been shown in male rats to impair wound healing by increased epidermal and connective tissue cell proliferation, polymorphonuclear leucocyte migration, myofibroblast density, and mast cell migration. In propranolol-treated animals, the volume density of blood vessels was increased, and vessels were more dilated [52]. In light of these findings, it is unclear what effect beta blockade has on our elderly patients who frequently are on beta blockers for coronary artery disease.

Vitamin E is a lysosomal stabilizer and is therefore an antiinflammatory compound. Vitamin E fits into the category of aspirin and dexamethasone because these agents have inhibitory effects on collagen synthesis and wound repair, and for this reason vitamin E should probably not be routinely recommended [53].

Contraction/scar formation

The wound next undergoes contraction and scarring as a natural progression. Fibroblasts from the previous phase have laid down collagen, and now the wound contracts. Studies have shown that the orientation of this collagen matrix determines wound attachment and contraction [54]. This phase is hormone dependent, and epidermal growth factor is one of the key chemical signals. In vitro it seems that epidermal growth factor loaded in collagen sponges resulted in significantly increased breaking strength and skin resilience [55]. Other key compounds active in wound contraction are TGF-β, mitogen-activated protein kinase, extracellular signal-regulated kinase, activin-linked kinase 5, and heparin sulfate–containing proteoglycans [56].

Factors that adversely affect contraction

The desired outcome is minimal scarring so that the wound has an excellent cosmetic appearance. There are chemical compounds that can adversely affect wound contraction. In an animal model, the animals on systemic isotretinoin had a significant delay in wound contraction when compared with control animals ($P < .001$). When the isotretinoin was discontinued, all the animals had complete wound healing within a week [57].

In a study with silver sulfadiazine (SSD), the placebo group, which received aqueous cream, healed in a significantly shorter time ($P < .05$) than the control (saline) group. Wound contraction was delayed by saline and SSD. Nystatin and aloe vera, when added to SSD, reversed that effect. These data suggest that a dry wound heals slowly. Infection control without delay of wound healing is appealing, and clinical trials are planned [58].

Isoform nitric oxide is useful in wound healing; however, superoxide levels, as found in excessively high levels of nitric oxide in the wound, impair wound healing [59].

Nutrition is important for this contraction phase because collagen is essentially a protein. In one animal study, open wounds contracted more slowly in the malnourished group. Matching these observations with histopathologic findings based on serial observations in these same animals, the differences between the contraction of open wounds in poorly nourished animals and in the control group seem to be associated with delay in the formation and the poor quality of granulation tissue in the malnourished animals [60].

In some cases, it is desirable that certain wounds do not contract. In an in vitro study using β_2-adrenergic receptor activation, these activators markedly decreased keratinocyte migration and may have some future clinical usefulness in preventing unwanted wound contraction in burn and trauma patients [61].

Wounds that are perpendicular to the lines of Langer are well known to have increased scarring. A novel approach by one author in Cairo, Egypt was to use botulinum toxin type A to prevent widening of perpendicular facial wounds [62].

Epithelialization

This phase is analogous to what occurs in fibroproliferation, with the notable differences being that the main work is done by keratinocytes and not fibroblasts, and the location of the work being done on the surface of the wound. Moist, non-occlusive dressings do not remove the surface that the wound is trying to lay down. Simple gauze moistened by saline or lime solution can serve as dressings but if not remoistened before removal can harm the delicate epithelial layer. It is more advantageous to apply some sort of ointment to prevent drying. Antibiotic ointment is classically used; the antibiotic component is not relevant for wound healing per say but may serve to keep bacterial counts down [63–66].

Factors that adversely affect epithelialization

With respect to keratinocytes, Biolex, Shur-Clens, and Techni-Care, were the least toxic to keratinocytes (toxicity index 0); hydrogen peroxide, modified Dakin's solution, and povidone (10%) were found to be the most toxic (toxicity index 100,000) [42].

Dressings can adversely affect epithelialization by removal of keratinocytes that are attempting to heal the wound. Depending upon the wound and purpose for the dressing, one must remember that wet-to-dry dressings have a place in debriding certain wounds. In vitro experiments reveal that dressings that are silver based have been found to be cytotoxic and should not be used in the absence of infection. Alginate dressings demonstrate high calcium concentrations, markedly reduced keratinocyte proliferation, and affected keratinocyte morphology [67].

We live in a nation in which people are living longer. In healthy humans, aging leads to delayed epithelialization. No effect of age on collagen

synthesis was noted, although accumulation of wound noncollagenous protein was decreased. This decrease may impair the mechanical properties of scarring in aged humans [68].

Smokers have been clinically noted to have delayed wound healing. There are deleterious effects of nicotine on wound reepithelialization, and this suggest that smoking may delay wound healing via a nicotinic receptor-mediated pathway [69].

Scar remodeling

Now begins the phase in which the collagen has been synthesized, the wound has contracted, and the wound undergoes remodeling. A role for collagen phagocytosis and intracellular degradation by fibroblasts during remodeling activity has been suggested by studies on several connective tissues characterized by high rates of collagen turnover and remodeling [70]. In addition, myofibroblasts differentiate to remodel the scar. Myofibroblast differentiation is a complex process, regulated by at least a cytokine (TGF-β1), an extracellular matrix component (the ED-A splice variant of cellular fibronectin), and the presence of mechanical tension. The myofibroblast is a key cell for the connective tissue remodeling that takes place during wound healing and fibrosis development [71]. Once remodeling is complete, in a process that occurs over several weeks, the wound achieves its final appearance.

Factors that adversely affect remodeling

Remodeling is dependent on the fibroblast classes, so nutrition and the patient's age should have the most important influence on the finished scar product. The age-associated healing delay in the rat may not be related to the appearance or abundance of distinct myofibroblast or apoptotic cell populations. Proteolysis may have a significant role in delayed wound healing in aged animals [58].

Given its importance in restoring health, it is not surprising that the care of soft tissue wounds is an extremely active area of research and development. Given the above framework of the phases of wound healing, an understanding of these new frontiers will help the clinician to evaluate new products and treatments as they emerge, and thus improve wound care.

Hemostasis

For most wounds, this phase is complete by the time a physician inspects the wound. For the minority of patients with severe wounds, treatments to promote the cessation of bleeding are of upmost importance. Many of these treatments are time honored and, like direct pressure, can be singularly effective [72]. Intensive research into dressings that have improved hemostatic properties as compared with gauze has yielded two excellent candidates, the Hemcon dressing (Portland, OR) and a fibrinogen/thrombin containing dressing. The Hemcon dressing is the only one commercially available

[73]. Although the tourniquet is an ancient medical device, it seems to be poised to make a comeback as a method of emergency hemorrhage control. Extensive use of the Combat Application Tourniquet (North American Rescue Products, Greenville, SC) by the United States military in ongoing conflicts and the positive risk-to-benefit ratio of hemostatic tourniquets suggest that tourniquets will be one of the medical advances that transitions from the military to civilian health care [74]. In addition to improved devices, research into pharmacologic approaches to promoting hemorrhage control has identified recombinant activated factor VII as a potentially useful drug [75]. Ongoing prospective, randomized, blinded, multicenter trials of recombinant-activated factor VII should serve to better inform the use of this drug for patients without inborn errors of the coagulation system.

Tissue oxygenation

The most direct approach to addressing wound ischemia involves the use of hyperbaric therapy to deliver oxygen to wounded tissues. This approach has proven useful, but it is beyond the care typically delivered by emergency physicians. The costs and facilities involved in hyperbaric therapy have driven innovation in direct delivery of oxygen to tissues. Among promising wound treatments in this area is a dressing system that produces molecular oxygen through the enzymatic consumption of hydrogen peroxide solution [76]. Other topical oxygen delivery systems, such as dressings and garments that are designed to be charged with gaseous oxygen and then contain the gas around the wound, have been described. Ambient or low-pressure oxygen is not equivalent to hyperbaric oxygen, and in the absence of evidence of efficacy, these technologies must be considered as unproven.

Edema

The negative effect of edema on wounds is not well understood at a mechanistic level, and hence research in this area is less developed. Until recently, few therapeutic options existed to manage edema directly. More recently, negative pressure therapy has undergone an explosion in interest. The expense and complexity of even the home health care device limits the applicability of this device to only the most challenging of wounds for outpatient care. There exists little experimental evidence for the mechanism of action of topical negative pressure therapy, although there is no shortage of theories. Preclinical and clinical studies of such mechanisms of action offer the potential to greatly inform the development of future approaches to wound care based on a sound understanding of the pathophysiology of edema [77].

Prevention of infection

Perhaps no area of wound care research has remained as active for as long as investigations of treatments to prevent and cure wound infection.

Although high-risk wounds generally indicate systemic antibiotics, research has focused on the application of local treatments to lower risk wounds in the effort to prevent the generally low rate of infection seen in uncomplicated wounds. In general, research has sought to balance the potential for these agents to retard wound healing with the positive effects of reduced bioburden and lower risk of infection [78]. Research has shown povidone-iodine to be of potential use in this respect. In addition, several studies have attempted to quantify the effect of antimicrobial creams and ointments on the incidence of wound infection. Many of these studies do not have sufficient power to make strong statements regarding the slight differences expected in infection rate. A notable exception was a study by Dire and colleagues [79], who found neomycin sulfate/bacitracin/polymyxin B sulfate ointment to be efficacious. Recent work by Anglen [80] highlighted the therapeutic potential of addition of castile soap to irrigation solutions but also highlighted the difficulty in demonstrating efficacy even in injuries where the infection risk is relatively high. Many factors can be considered in the assessment of wounds for risk of infection, leading the decision to deploy topical antimicrobials to be idiosyncratic to the provider. Perhaps the most useful method for prevention of wound infection is a rigorous method for assessing such risk. Lammers and colleagues [81] present an evidence-based decision support tool that may be of use in bringing rigor to this area of clinical judgment.

Inflammatory mediators

In the attempt to improve wound care, significant developmental effort has been focused on the initiation of the inflammatory cascade in response to wounding. For the acute wound, management of inflammation is not necessary. Chronic wounds may benefit from research into the modification of inflammation. Control of inflammation is directly achieved through removal of foreign matter and bacteria that induce such prolonged inflammatory states, but factors that induce transition to reepithelialization and angiogenesis, such as topical growth factors [82], autologous platelet-rich plasma [83], and matrix metalloprotease inhibitors [84], have also shown promise in promoting wound healing. Many of these factors can enhance wound healing in animal models of acute wound healing, although their expense and potential complications usually preclude use when wound healing is expected to progress normally.

Regenerative medicine

Perhaps the last frontier in the treatment of injury and disease is the modification of the process of healing beyond scar formation to tissue regeneration. This regenerative approach (also termed tissue engineering) seeks to recapitulate the generation of tissue that occurs during embryogenesis and

development and avoid the process of scar formation. Although research and development of regenerative products has focused on severe wounds and disease states, these approaches will be applicable to wounds of any severity with the decision to deploy regenerative medicine based largely on the associated costs and risks. Research and development addressing regeneration has been focused on three related technologies: extracellular matrix (the acellular components of tissue), growth factors (signaling molecules that direct the actions of cells), and stem cells (cells capable of development into various mature cell types). The most mature of these technologies is extracellular matrix, with commercial products already available. Current research seeks to expand the use of extracellular matrix products, to investigate and optimize the underlying mechanisms of action, and to improve usability of these products [85]. Intermediate in maturity are growth factor products, including the currently available recombinant PDGF. Research is progressing rapidly on an entire alphabet soup of growth factors for application to soft tissue wounds (reviewed in Ref. [82]). Many of these (eg, VEGF and epidermal growth factor) have shown promise in preclinical testing, but FDA approval remains a significant barrier for many of these products.

Much ink has been spilled regarding the application of stem cells to human disease, and the future of this technology is bright. It is important to differentiate between fetal stem cells, with their high potential and controversial status, and adult stem cells, which have less potential but are not controversial from religious, ethical, or moral points of view. Adult mesenchymal stem cells can be derived from various patient tissues and, as autologous cells, avoid the issues surrounding transplant incompatibility. Interest is high in developing stem cells from fat, placenta, and cord blood, and preclinical data exist for the application of bone marrow–derived [86] and muscle-derived [87] cells.

Summary

Wound healing is a complex interchange, orchestrated between cellular components that play their respective parts signaled by and mediated by different cellular instruments of healing. When healing is flawless, the final product is a thing of beauty. When healing is delayed, interrupted, or excessive, then unsightly scars of chronic painful wounds that are frustrating to the patient and physician occur.

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