The Physiology of Wound Healing

It’s important to understand the science behind treatment decisions.

Objectives

1. Educate about the phases of wound healing
2. Contrast acute vs. chronic wounds
3. Introduce the biochemistry of the wounds
4. Elucidate wound bed preparation
5. Learn how to control the micro and macro wound environments

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Following this article, an answer sheet and full set of instructions are provided (p. 194).—Editor

The specialty of wound management is evolving; clinicians are faced with many treatment choices including active dressings, biologic skin substitutes, and negative pressure wound therapy, among others. Evidence-based research remains the mainstay for choosing appropriate, disease-specific algorithms and an intimate knowledge of wound science is mandatory. The following article represents an overview of basic wound healing principles; mastery of these concepts will lead the clinician to scientifically “logical” treatment choices.

Phases of Wound Healing

Wounds represent a complicated series of biochemical reactions and processes that create an orderly healing cascade. Scientists study acute wounding by viewing the processes as three distinct phases; however, wound healing actually progresses along a continuum.

Inflammatory Phase

This phase occurs in the first 1-4 days of injury and results in the formation of a fibrin clot. Platelets remain the first cell type mobilized to support the wounded area; these cells release platelet-derived growth factor (PDGF). Neutrophils and macrophages are predominant during the inflammatory phase, as well as low levels of enzymes called proteases. These chemical mediators help break down the extra-cellular matrix (ECM) so that a new matrix can be formulated.

Proliferative Phase

This phase occurs between 4-21 days and fibroblasts predominate. During this period there is tumultuous...
The derailment of normal wound healing is predicated upon many events, including patient factors, physical factors, macro-environmental and micro-environmental factors; thus they require an evidence-based, holistic approach to diagnosis and treatment. A complete history and physical remains paramount and the underlying wound etiologies must be elucidated prior to treatment, if possible. Patients should be questioned in detail about the wound itself, including initial cause, duration, and previous treatments, if any.

Important results have been gleaned from research evaluating acute and chronic wound fluids. Acute wound fluid possesses active cells that cultivate the wound milieu. This includes cells that remain viable while possessing the ability to respond to growth stimuli. Scientists observe growth factors in sufficient quantities facilitating cell proliferation, migration, and tissue synthesis. The wound environment remains nurturing, leading to predictable wound closure.

High levels of growth factors function in balance amidst low levels of inflammatory cytokines and proteases such as matrix metalloproteases. Matrix Metalloproteases (MMP's) represent a family of 20 structurally-related protein-degrading enzymes produced by every cell in the wound. MMP's require calcium for structural conformation and zinc ions for activity. Researchers confirm MMP's undergo synthesis in response to tissue injury when mediated by certain biochemical signals, including inflammatory cytokines.

Tissue inhibitors of metalloproteases (TIMP's) normally control tissue levels of these proteases. In low concentrations, scientists hypothesize MMP's play a positive and essential role in acute wound healing. Chronic wound fluid, however, contains senescent cell types, low levels of growth factors, high level of inflammatory cytokines and very high levels of proteases. These concentrations lead to a hostile environment, further destroying proteins and other biochemical mediators required for orderly wound closure. The chronic wound fails to move forward into the proliferative and remodeling phases and therefore remains “stuck” in the inflammatory phase. Faulty receptor sites required to capture essential growth factors may also characterize chronic wound pathology. The complexity of wound biochemistry remains far-reaching and beyond the scope of this manuscript; the author has supplied references at the end of this text for further study.

Bacterial Bio-burden and Wound Healing

Increases in bacterial bio-burden can create impediments to healing. All wounds are contaminated or colonized with bacteria that are non-replicating and replicating respectively; however, bacteria at these levels do not invade the host. Contaminated or colonized wounds demonstrate bacterial levels that will not limit progression of the normal healing cascade. Methicillin-resistant Staphylococcus aureus (MRSA) is now community-acquired and patients residing in nursing facilities or with histories of recent hospitalization are likely to colonize this bacterium at wound surfaces. Swab cultures detecting surface bacteria may be misleading and could perpetuate injudicious use of antibiotics. Practitioners may swab wounds without first removing devitalized necrotic tissue; results are reported in a non-quantitative manner.

Unfortunately, when wounds become critically colonized or infected, quantitative biopsies reveal organisms at levels of greater than 10^5 CFU/gm tissue; a concentration proven to compromise normal wound healing. There are numerous reasons for this phenomenon: increases in bacterial load utilize oxygen and nutrients normally required to promote healing. Bacteria also create enzymes that may degrade proteins such as growth factors. Therefore, reducing excessive bacterial burden remains paramount. Additionally, beta-hemolytic streptococci at much lower levels may present similar consequences. Research supports the need for bacterial balance.

Approximately 20% of patients do not mount a physiological response to infection, especially in the immunocompromised diabetic population. Clinical judgment is required to detect subtle differences at wound sites, including friable granulation tissue, increased drainage, or foul odor, among others. Gardner observed, however, that clinical signs and symptoms in chronic wounds were frequently absent, Continued on page 189
Healing...

making the diagnosis elusive. New research may elucidate the mechanisms behind lack of erythema in diabetic patients. This phenomenon is due to local vasodilatation, and the inactivation of nitric oxide by advanced glycosylation endproducts may be the pathophysiological mechanism that underlies diminished expression of this symptom.

Robson demonstrated that systemic antibiotics failed to reach adequate tissue levels in chronic granulation tissue; therefore, these drugs may be of limited value in reestablishing bacterial balance in these wound types. Clinicians should take heed: This study fosters the use of topical antimicrobials in conjunction with systemic therapy where appropriate.

**Wound Bed Preparation**

Wound Bed Preparation (WBP) represents a paradigm shift in wound management. This methodology fosters removal of healing impediments, thus initiating the repair process and restoration of healthy granulation tissue.

Clinicians define WBP as the management of a wound in order to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures.

This concept extends the holistic approach to wound management, removing barriers to healing, establishing healthy granulation tissue, and stimulating a well-vascularized wound bed. WBP combines a number of important concepts into a systemic approach to help restore wound stability. The acronym TIME encapsulates the basic principles of WBP as follows:

- **T** equals tissue, non-viable or de-

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Debridement

Clinicians perform debridement in several ways, including surgical, enzymatic, autolytic, mechanical, and biologic (larvae/maggot therapy). Performance of debridement fosters the practitioner’s ability to evaluate the wound, including undermining abscesses, or bone, tendon and muscle involvement. Research supports that debridement may be an independent predictor of healing\(^{11,12}\). The procedure facilitates removal of necrotic tissue, while stimulating production of growth factors and other biochemical processes. The goals of debridement remain consistent; removal of necrotic tissue while preserving healthy granulation tissue.

Biochemical Rationale Behind Advanced Treatment Protocols

Topical antimicrobials: Topical agents such as gentamycin, Neomycin, or Bacitracin may quickly create systemic resistance and remain persistent allergens\(^{13}\). Clinicians overwhelmingly embrace silver dressings and products containing cadexomer iodine. Unlike silver nitrate and silver sulfadiazine, which require repeated applications, new technologies such as nanocrystalline silver allow for consistent delivery over time. Silver maintains broad-spectrum antimicrobial activity against 150+ organisms, encompassing yeasts, molds and bacteria including MRSA and VRE. Cadexomer iodine polysaccharide beads contain 0.9% iodine and function by absorbing fluid while the iodine slowly releases. No evidence of bacterial resistance exists and the drug kills a broad range of organisms including MRSA.

Researchers agree that cases of bacterial resistance to silver remain unlikely due to the product’s complex mechanisms of action, including binding to and disruption of bacterial DNA, respiratory enzymes, and cell walls\(^{14}\).

Biochemical Modulators

Scientists agree that controlling proteases characterizes an important goal as part of a comprehensive wound healing algorithm.

ORC/Collagen (Promogran™ Matrix Wound Dressing) is a novel active chronic wound therapy. This product modulates and rebalances the microenvironment through binding and inactivation of proteases while protecting growth factors. As the matrix degrades, active endogenous and exogenous growth factors are released back into the wound bed.

Research suggests this matrix may reduce proteolytic activity in wound fluid by binding to MMP’s while protecting the biological activity of growth factors\(^{15}\). Clinicians liken this phenomenon to a “sponge” soaking up and inactivating MMP’s, while facilitating a protective effect on cytokines that these proteases would normally degrade. All chronic wounds, including diabetic foot ulcers, venous leg ulcers, and pressure ulcers may benefit from this product. Promogran Prisma™ (ORC/Collagen plus 1% silver (0.25% ionic silver) releases low levels of silver that will lower bio-burden early in treatment while protecting host cells, balancing proteases, and protecting active growth factors.

Skin Substitutes

Biologic skin substitutes are physiologic dressings that may signal growth factor activity. Derived from neonatal foreskin, products such as Apligraf™ and Dermagraft™ create temporary wound coverage while “bathing” the lesion with essential cytokines, mitigating pain and augmenting healing. Apligraf™ contains both dermis and epidermis, while Dermagraft™ represents a dermal matrix composed of fibroblasts. Cadaveric allograft may also be useful. Research consistently reports that this wound covering aids in limiting infection while decreasing water and electrolyte and protein loss. Pain is also reduced, allowing exercise, ambulation, and decreased incidence of contracture\(^{16}\). These products work most efficiently once the clinician has rebalanced the microenvironment, lowered bacterial bioburden, and facilitated granulation tissue via wound bed preparation.

Topical Growth Factors

Two types of topical growth factors presently exist for clinical use: autologous and recombinant. Blood-derived growth factors characterize the autologous platelet releasate variety and are applied in a solution. Conversely, recombinant growth factors are not derived from blood but are formulated through DNA technology; chemists glean a single growth factor isolate possessing similar biologic activity to the endogenous variety. Research supports that topically applied PDGF-bb (Regranex Gel™) adjunctively augments granulation tissue, angiogenesis, and epithelialization\(^{17}\). Continued on page 191
factors, and negative pressure wound therapy (NPWT), among others.

**Negative Pressure Wound Therapy**

Negative pressure wound therapy (NPWT) /VAC Therapy represents a significant advancement in wound management. This modality functions as an active dressing by manipulating the microenvironment; healing becomes stimulated through facilitation of chemical reactions and biochemical processes. NPWT/VAC Therapy is a non-invasive, active treatment that promotes moist wound healing by utilizing controlled, localized sub-atmospheric pressure. An even distribution of negative pressure results in a tissue tension/stress effect. Researchers and clinicians recognize the concept of tissue response to applied forces in relation to bone physiology (Wolfe’s Law).

The Ilizarov technique represents a practical application of this phenomenon. Furthermore, NPWT/VAC Therapy can function by actively removing extra-cellular debris. Foremost, this modality decreases peri-wound edema, thus increasing wound profusion and improving nutrition. This therapy creates collapse of the attached foam dressing, thus deforming underlying cells. The resultant changes in the expression of immediate-early genes leads to increases in cellular proliferation and protein synthesis. Treatments may create active wound contraction, decreased bacterial colonization, increased rates of granulation tissue formation and epithelialization, and stimulation of mitosis and angiogenesis.

The treatment functions adjunctively and does not replace appropriate wound care, surgical procedures, or antibiotic therapy. This modality creates a dynamic whereby the wound may improve to a point where less invasive procedures may become feasible.

There are many indications for NPWT/VAC, including chronic wounds, acute and/or traumatic wounds, dehiscence, diabetic and pressure ulcers, flaps and grafts, and partial thickness burns. Goals include decompression of interstitial spaces, minimization of infectious pathogens, optimization of healing environment, and increased perfusion. Furthermore, NPWT/VAC foster collection and quantification of volume loss and stabilization/bolstering of grafts to recipient sites.

NPWT/VAC function cost-effectively by reducing the numbers of dressing changes and costs related to extended care facilities, among others.

**Critical Assessment**

Due to the complexities of treating chronic non-healing lesions, clinicians must constantly re-evaluate and assess clinical wound features and un-
underlying co-morbidities while facilitating adjustments as required. Within a collaborative wound care center, monthly interdisciplinary meetings foster discussions concerning outliers and challenging cases.

Conclusions
Acute and chronic wounds represent wide biochemical variations and therefore should be approached differently. Clinicians must be intimately familiar with wound healing science in order to make rational treatment decisions. To this end, an algorithm that embodies a holistic and collaborative approach substantiated by evidenced-based protocols is mandatory. This includes debridement, infection control, optimized vascularity, off-loading, nutritional support, moisture control, cessation of smoking, and control of underlying co-morbidities, among others. These wound care practices aid in fostering wound bed preparation and facilitate the use of advanced wound therapies such as new topical antimicrobials, biochemical modulators, biologic skin substitutes, topically applied growth factors, hyperbaric oxygen, and negative pressure wound therapy.

NPWT helps remove stagnant wound fluid, and decreases peri-wound edema, while increasing wound nutrients. Additionally, this therapy creates collapse of the attached foam dressing, thus deforming underlying cells. The resultant changes in the expression of immediate-early genes leads to increases in cellular proliferation and protein synthesis.

It remains clear that knowledge of wound biochemistry may facilitate better treatment choices. Thought leaders envision a “litmus” test where wound biochemistry may one day be quantified and treatment fostered by biochemical benchmarks. Treatment decisions, however, are presently formulated based largely on clinical judgment. Wound care paradigms may soon include gene therapy and modulation of many biochemical entities yet to be discovered that may improve the quality of life and health of patients with chronic wounds.

References
Armstrong DG, Jude EB.: The role of matrix metalloproteases in wound healing.


Snyder RJ, Davis J.: Insights on physiology and pathophysiology of negative pressure wound therapy. Ostomy-Wound Management 2004;50(11A Suppl):2S-4S.


Snyder RJ: A holistic approach to understanding and addressing the wound microenvironment to facilitate healing. Wounds (Supplement).August 2005: 12-17.


Additional References
Choose the single best response to each question listed below.

1) The phases of acute wound healing include:
   A) Proliferative phase
   B) Inflammatory phase
   C) Remodeling phase
   D) All of the above

2) The primary goal of the inflammatory phase of acute wound healing is to:
   A) break down extra-cellular matrix
   B) increase wound tensile strength
   C) flood the wound with fibroblasts
   D) stimulate angiogenesis

3) Platelet-derived Growth Factor is released by all of these cells except:
   A) Keratinocytes
   B) Neutrophils
   C) Platelets
   D) Smooth muscle cells

4) The first cell noted in the inflammatory phase is the:
   A) Neutrophil
   B) Platelet
   C) Macrophage
   D) Fibroblast

5) The prominent cell of the proliferative phase is the:
   A) Macrophage
   B) Fibroblast
   C) Smooth muscle cell
   D) Leukocyte

6) The following are goals of the proliferative phase except:
   A) Granulation tissue
   B) Collagen formation
   C) Angiogenesis
   D) Epithealization

7) The remodeling phase is responsible for what process in wound healing?
   A) Increasing tensile strength
   B) Decreasing tensile strength
   C) Breaking down the extra-cellular matrix
   D) Producing monocytes

8) Benefits of negative pressure wound therapy include all except:
   A) removes extra cellular debris
   B) removes exudate causing dry wound
   C) decreases periwound edema
   D) creates tension/stress effect

9) Below are all examples of chronic wounds except:
   A) Pressure wound
   B) Venous insufficiency wound
   C) Surgical wound
   D) Pyoderma gangrenosa wound

10) Factors that impair normal wound healing include:
    A) Patient

11) Matrix Metalloproteases (MMP) are produced by:
    A) Fibroblasts
    B) Neutrophils
    C) Macrophages
    D) All the above

12) MMP’s require which elements for structural confirmation and activity?
    A) Iron
    B) Lead
    C) Carbon and iron
    D) Calcium and zinc

13) High levels of MMP are noted in all wounds except:
    A) Chronic wounds
    B) A fresh surgical incision
    C) Long-standing venous ulcer
    D) Chronic diabetic foot ulcer

14) Chronic wounds are stagnant in which phase of wound healing?
    A) Proliferative
    B) Inflammatory
    C) Remodeling
    D) Healing

15) Signs of increased bioburden include all except:
    A) Epithealization
    B) Increased exudates
    C) Increased odor
    D) Increased friability of granulation tissue

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16) The goals of VAC therapy include all except:
   A) decompression of interstitial space
   B) minimization of infectious pathogens
   C) optimized healing
   D) decreased wound perfusion

17) All of the following topical antimicrobials presently can create systemic resistance except:
   A) Silver
   B) Gentamycin
   C) Bacitracin
   D) Neosporin

18) Benefits of Promogran (ORC/Collagen) include:
   A) Hemastasis
   B) Protection of active growth factors
   C) Ability to inactivate/ degrade proteases
   D) All the above

19) Prisma (Collagen/ORC/silver-ORC) offers which added benefit to Promogran:
   A) Protects growth factors
   B) Balances proteases
   C) Lowers bio-burden
   D) Protects host cells

20) Benefits of Hyperbaric oxygen therapy include:
   A) Up-regulation of PDGF receptor sites
   B) Fibroblast proliferation
   C) Cellular mitosis
   D) All the above
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(Joseph and Kosinski)

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3. A B C D  
4. A B C D  
5. A B C D  
6. A B C D  
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(Snyder and Sigal)

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3. A B C D  
4. A B C D  
5. A B C D  
6. A B C D  
7. A B C D  
8. A B C D  
9. A B C D  
10. A B C D

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