

# Wound healing

November 4, 2004

## Wound healing

- Wound healing is the process of repair that follows injury to the skin and other soft tissues.
- Healing is the interaction of a complex cascade of cellular events that generates resurfacing, reconstitution, and restoration of the tensile strength of injured tissue.
- Under the most ideal circumstances, healing is a systematic process, traditionally explained in terms of 3 classic phases: inflammation, proliferation, and maturation.

## Wound healing

- **The inflammatory phase:** a clot forms and cells of inflammation debride injured tissue.
- **The proliferative phase:** epithelialization, fibroplasia, and angiogenesis occur; additionally, granulation tissue forms and the wound begins to contract.
- **The maturation phase:** Collagen forms tight cross-links to other collagen and with protein molecules, increasing the tensile strength of the scar.

## I. Inflammatory Phase

- **Immediate to 2-5 days**
- **B Hemostasis**
- Vasoconstriction
- Platelet aggregation
- Thromboplastin makes clot
- **C Inflammation**
- Vasodilation
- Phagocytosis

## II. Proliferative Phase

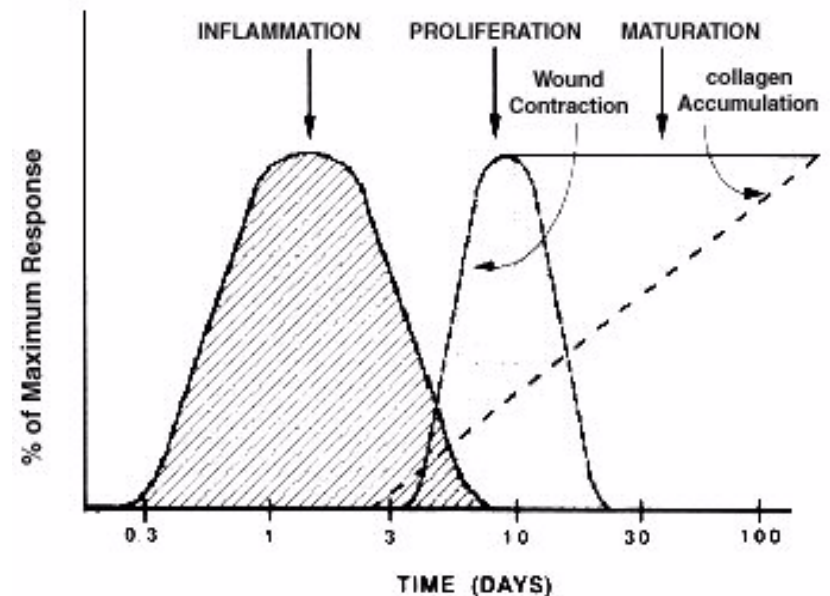
- 2 days to 3 weeks
- **B) Granulation**
  - Fibroblasts lay bed of collagen
  - Fills defect and produces new capillaries
- **C) Contraction**
  - Wound edges pull together to reduce defect
- **D) Epithelialization**
  - Crosses moist surface
  - Cell travel about 3 cm from point of origin in all directions

## III. Remodeling (maturation) Phase

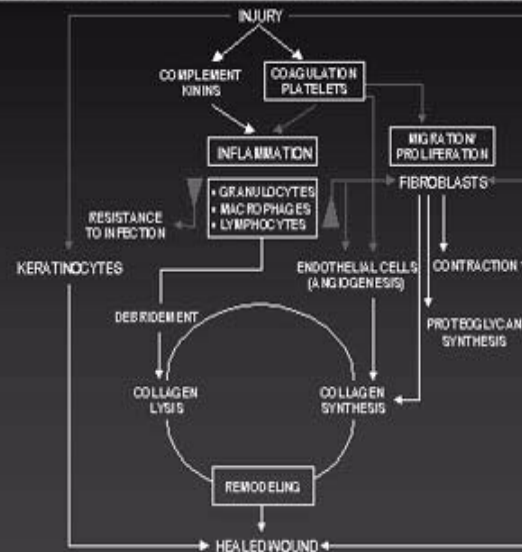
- 3 weeks to 2 years
- **B) New collagen forms which increases tensile strength to wounds. Scar tissue is only 80 percent as strong as original tissue**

## Scar Formation

- The process of wound healing is essentially similar in all tissues and is relatively independent of the mode of injury; however, slight variation in the relative contribution of the different elements to the overall result may occur.
- The final product of the healing process is a **scar**. This relatively avascular and acellular mass of collagen serves to restore tissue continuity, strength and function.
- **Delays** in the healing process cause the prolonged presence of wounds, while
- **abnormalities** of the healing process may lead to abnormal scar formation.



## SCHEMATIC REPRESENTATION OF WOUND HEALING



Adapted with permission from Zabel DD and Hunt TK. *Perspect Colon Rectal Surg.* 1993;6:192. Thieme - Medical Publishers, New York.

## Inflammatory Phase

- The body responds quickly to any disruption of the skin's surface.
- The early events of wound healing are characterized by a vascular and cellular response to injury.
- An incision made through a full thickness of skin causes a disruption of the microvasculature and immediate hemorrhage.
- Within seconds of the injury, blood vessels constrict to control bleeding at the site. Platelets coalesce within minutes to stop the bleeding and begin clot formation.

## Inflammatory phase

Following incision of the skin, a 5- to 10-minute period of vasoconstriction ensues, mediated by epinephrine, norepinephrine, prostaglandins, serotonin, and thromboxane.

Vasoconstriction causes temporary blanching of the wound and functions to reduce hemorrhage immediately following tissue injury, aid in platelet aggregation, and keep healing factors within the wound.

## Inflammatory phase

- Endothelial cells retract to expose the subendothelial collagen surfaces; platelets attach to these surfaces.
- Adherence to exposed collagen surfaces and to other platelets occurs through adhesive glycoproteins: fibrinogen, fibronectin, thrombospondin, and von Willebrand factor.

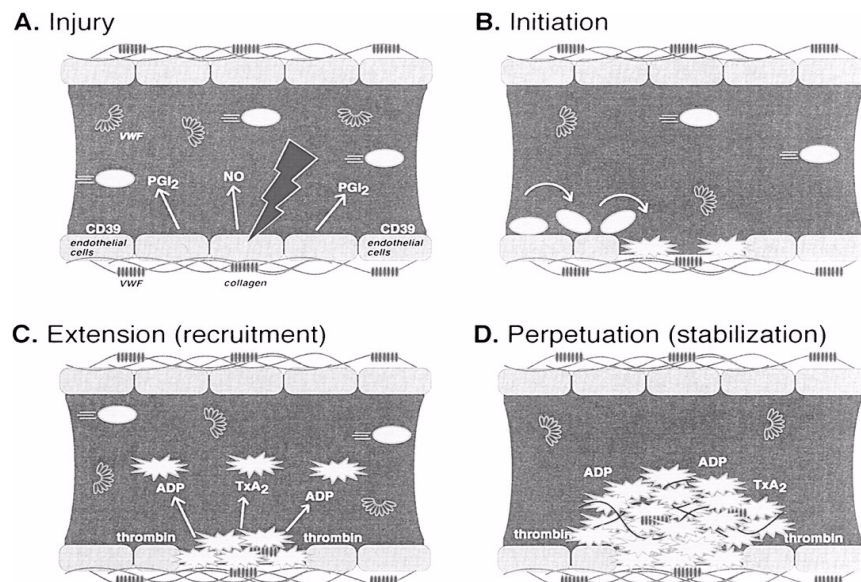
## Inflammatory Phase

- Platelets also release factors that attract other important cells to the injury. Neutrophils enter the wound to fight infection and to attract macrophages. Macrophages break down necrotic debris and activate the fibroblast response.
- The inflammatory phase lasts about 24 hours and leads to the proliferation phase of the healing process.

## Inflammatory phase

- The aggregation of platelets results in the formation of the primary platelet plug. Aggregation and attachment to exposed collagen surfaces activates the platelets. Activation enables platelets to degranulate and release chemotactic and growth factors, such as platelet-derived growth factor (PDGF), proteases, and vasoactive agents (eg, serotonin, histamine).

### Stages in platelet plug formation



## Inflammatory phase

- The coagulation cascade occurs by 2 different pathways.
- The intrinsic pathway begins with the activation of factor XII (Hageman factor), when blood is exposed to extravascular surfaces.
- The extrinsic coagulation pathway occurs through the activation of tissue factor found in extravascular cells in the presence of factors VII and VIIa.

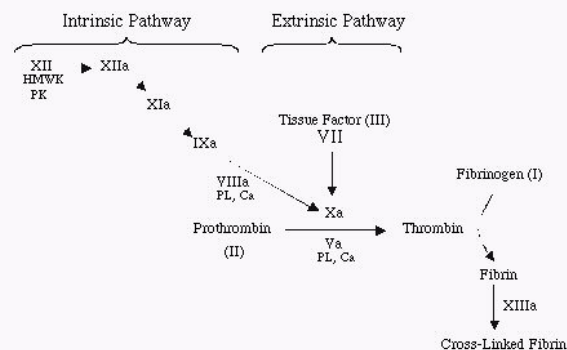
## Inflammatory phase

- Both pathways proceed to the activation of thrombin, which converts fibrinogen to fibrin.
- **The fibrin product is essential to wound healing and is the primary component of the wound matrix into which inflammatory cells, platelets, and plasma proteins migrate. Removal of the fibrin matrix impedes wound healing.**

## Inflammatory phase

- In addition to activation of fibrin, thrombin facilitates migration of inflammatory cells to the site of injury by increasing vascular permeability. By this mechanism, factors and cells necessary to healing flow from the intravascular space and into the extravascular space.

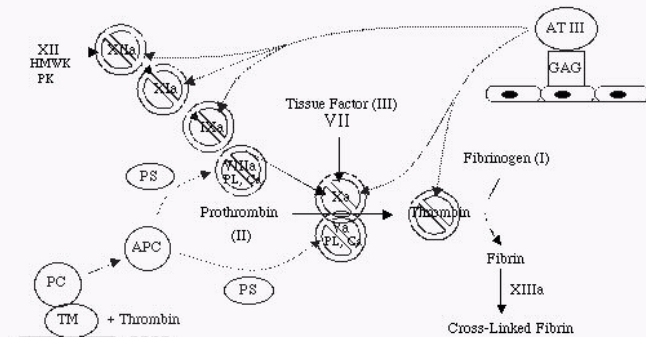
## Review of Coagulation Pathway



## Inflammatory phase

- The result of platelet aggregation and the coagulation cascade is clot formation.
- Clot formation is limited in duration and to the site of injury.
- Clot formation dissipates as its stimuli dissipate. Plasminogen is converted to plasmin, a potent enzyme aiding in cell lysis.
- Clot formation is limited to the site of injury because uninjured nearby endothelial cells produce prostacyclin, an inhibitor of platelet aggregation. In the uninjured nearby areas, antithrombin III binds thrombin, and protein C binds factors of the coagulation cascade, namely, factors V and VIII.

## Review of Anticoagulation Pathways



## Proliferation Phase

- On the surface of the wound, epidermal cells burst into mitotic activity within 24 to 72 hours. These cells begin their migration across the surface of the wound.
- Fibroblasts proliferate in the deeper parts of the wound. These fibroblasts begin to synthesize small amounts of collagen which acts as a scaffold for migration and further fibroblast proliferation.

## Proliferation Phase

- Granulation tissue, which consists of capillary loops supported in this developing collagen matrix, also appears in the deeper layers of the wound. The proliferation phase lasts from 24 to 72 hours and leads to the fibroblastic phase of wound healing.

## Proliferation Phase

- Four to five days after the injury occurs, fibroblasts begin producing large amounts of collagen and proteoglycans.
- Collagen fibers are laid down randomly and are cross-linked into large, closely packed bundles.

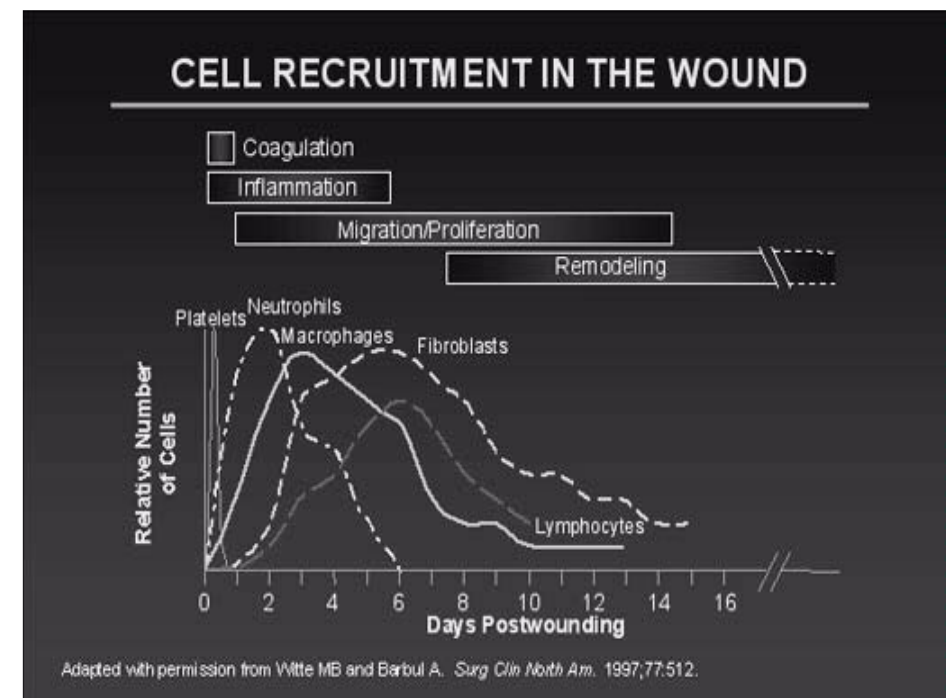
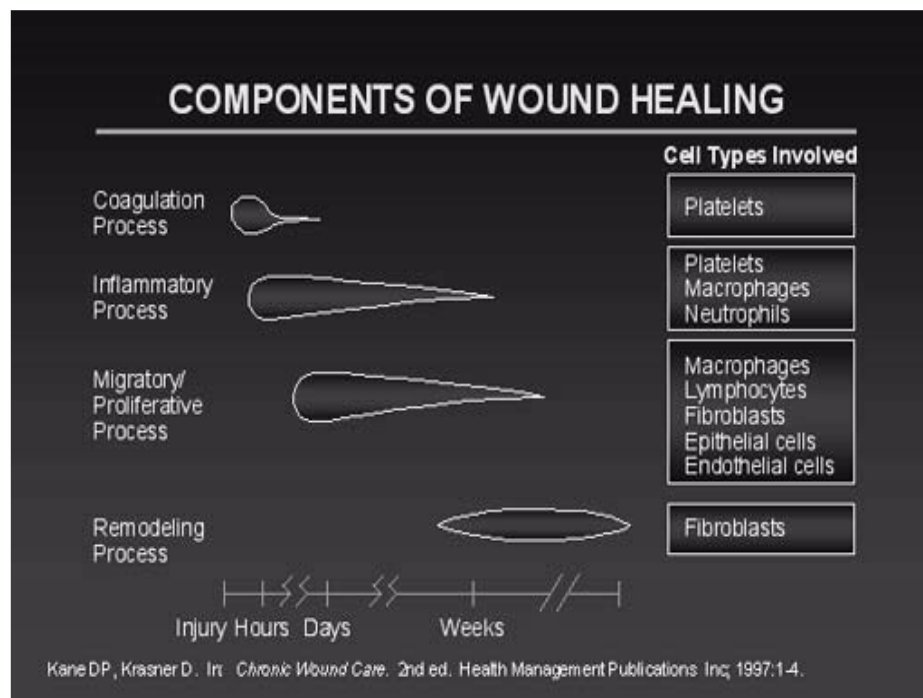


## Proliferation Phase

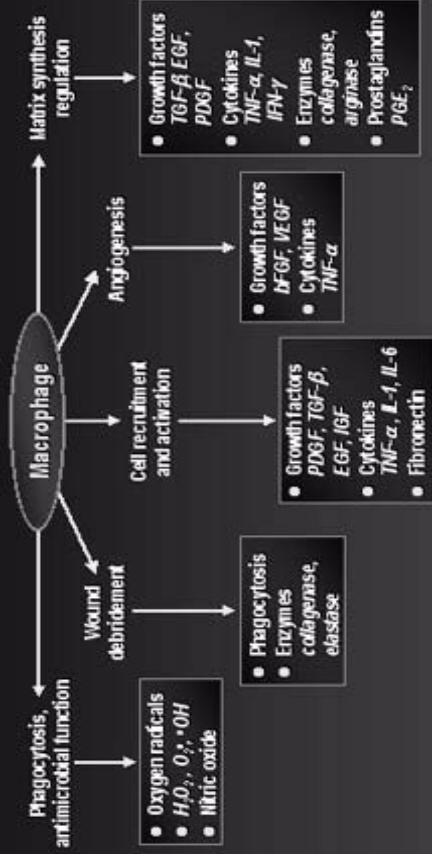
- Proteoglycans appear to enhance the formation of collagen fibers, but their exact role is not completely understood. Within two to three weeks, the wound can resist normal stresses, but wound strength continues to build for several months. The fibroblastic phase lasts from 15 to 20 days and then wound healing enters the maturation phase.

## Maturation Phase

- During the maturation phase, fibroblasts leave the wound and collagen is remodeled into a more organized matrix.
- Tensile strength increases for up to one year following the injury. While healed wounds never regain the full strength of uninjured skin, they can regain up to 70 to 80% of its original strength.

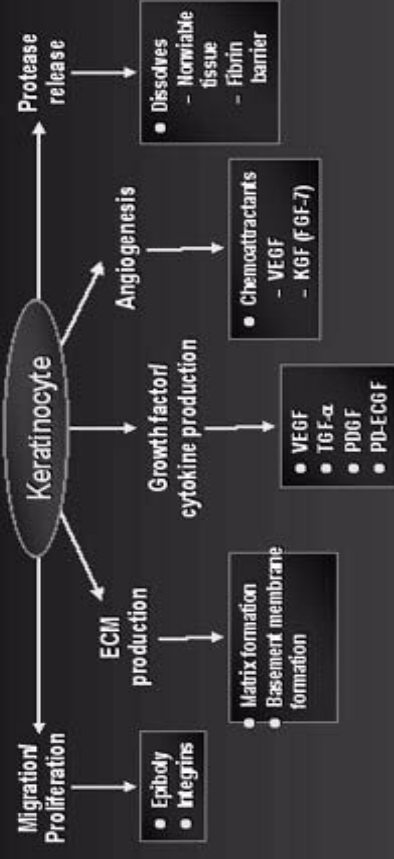


## ROLE OF MACROPHAGES IN WOUND HEALING



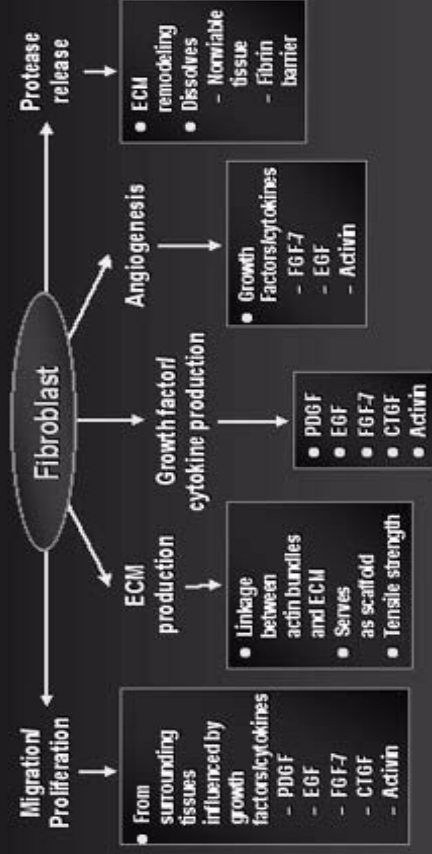
Adapted with permission from Witte MB and Barbul A. *Surg Clin North Am.* 1997;77:513.

## ROLE OF KERATINOCYTES IN WOUND HEALING



ECM = extracellular matrix.

## ROLE OF FIBROBLASTS IN WOUND HEALING



ECM = extracellular matrix.

## MIGRATION/PROLIFERATION Angiogenesis

- Formation of vessels
  - Begin as endothelial cell buds
  - Progress toward wound space, following oxygen gradient
  - Immature vessels differentiate into capillaries, arterioles, and venules
  - Macrophages and keratinocytes provide angiogenic stimuli

Hurt TK, Zabel DD. In: *Textbook of Critical Care*. 3rd ed. WB Saunders Co; 1995:1475-1486. Martin P. *Science*. 1997;276:79.



## MIGRATION/PROLIFERATION

### Epithelization

- Epidermal covering (keratinocytes) reconstituted from wound margin and hair follicle remnants
- Keratinocytes migrate across wound
- During and after migration, differentiation and stratification of neodermis occur
- Epithelization aided by moist environment

Martin P. et al. *Prog Growth Factor Res.* 1992;4:25-44.  
Martin P. *Science.* 1997;276:75-81.

## MIGRATION/PROLIFERATION

### Fibroplasia

- Fibroblasts
  - Migrate into wound site and replicate
  - Dominant cell type at wound edge
  - Synthesize and deposit collagen and proteoglycans
- Matrix deposition dependent on oxygen and substrate availability as well as growth factors

Hurt TK, Zabel DD. *Textbook of Critical Care.* 3rd ed. WB Saunders Co; 1995:1475-1486.  
Witte MB, Barbul A. *Surg Clin North Am.* 1997;77:509-528.

## HEALING RETARDED BY SEVERAL FACTORS

- Ischemia
- Dry wound environment
- Infection
- Foreign bodies
- Anti-inflammatory therapy
- Nutritional deficiency

Haimowitz JE, Margolis DJ. In: *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*. 2nd ed. Health Management Publications Inc, 1997:49-56.  
Hurt TK, Zabel DD. In: *Textbook of Critical Care.* 3rd ed. WB Saunders Co, 1995:1475-1486.

## REMODELING

- Changes in matrix composition over time



Adapted with permission from Greenfield LJ, ed. *Surgery.* 2nd ed. Lippincott-Raven Publishers, 1997.

## REMODELING

Changes in physical properties of extracellular matrix



Adapted with permission from Madden JW and Peacock EE Jr. *Am Surg.* 1971;17:4-517.

## HEALING PROCESS: ACUTE WOUNDS

- Sequence completed in continuous and expected time frame
- Usually achieved with few or no complications
- Overreaction in acute wound healing
  - Keloids
  - Hypertrophic scars

Kane DP, Krasner D. *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*. 2nd ed. Health Management Publications Inc; 1997:1-4. Hurley J. In: Krasner D, Kane D. *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*. 2nd ed. Health Management Publications Inc; 1997:195.

## CHRONIC WOUNDS

- Failure or delay of healing component(s)
- Unresponsiveness to normal growth regulatory signals
- Associated with repeated trauma, poor perfusion/oxygenation, and/or excessive inflammation
- Systemic disease
- Genetic factors

Kane DP, Krasner D. In: *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*. 2nd ed. Health Management Publications Inc; 1997:1-4. Hasan A et al. *J Dermatol Sci.* 1997;16:59-66.

## LOCAL FACTORS AFFECTING WOUND HEALING

- Mechanical injury
- Infection
- Edema
- Ischemia/necrotic tissue
- Topical agents
- Ionizing radiation
- Low oxygen tension
- Foreign bodies

Kerstein MD. *Adv Wound Care.* 1997;10:30-36. Waldorf H, Farkas J. *Adv Dermatol.* 1995;10:77-96.

## REGIONAL FACTORS AFFECTING WOUND HEALING

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- Arterial insufficiency
- Venous insufficiency
- Neuropathy

Hurt TK, Zabel DD. In: *Textbook of Critical Care*, 3rd ed. WB Saunders Co; 1995:1475-1486.  
Stotts NA, Wipke-Tevis D. In: *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*, 2nd ed. Health Management Publications Inc; 1997:64-72.

## SYSTEMIC FACTORS AFFECTING WOUND HEALING

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- Inadequate perfusion
- Inflammation
- Nutrition
- Metabolic diseases
- Immunosuppression
- Connective tissue disorders
- Smoking

## MANAGEMENT OF CHRONIC WOUNDS: Local and Regional

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- Prevent or treat infection
- Debridement as necessary
- Apply occlusive dressings
- Pain management
- Bilayered living skin construct (eg, APLIGRAF™)
- Surgical intervention

Kerstein MD. *Adv Wound Care*. 1997;10:30-36.

## MANAGEMENT OF CHRONIC WOUNDS: Systemic

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- Correct or alleviate circulatory deficiencies
- Correct nutritional deficiencies
- Monitor blood glucose levels
- Control hypertension and edema
- Other

Kerstein MD. *Adv Wound Care*. 1997;10:30-36.

## FUTURE OF WOUND HEALING

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- Continued research
  - Elucidation of signals/growth factors involved in:
    - epithelization
    - wound contraction and scarring
    - angiogenesis
- Tissue engineering
- Gene therapy

Martin P., *Science*, 1997;276:75-81.  
Phillips T.J., *J Dermatol Surg Oncol*, 1993;19:794-800.